INTRAMOLECULAR CYCLIZATIONS OF SUBSTITUTED 5-HEXENYL RADICALS

A THESIS

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G. PHILLIPOU, B.Sc.(HONS), M.Sc.

Department of Organic Chemistry

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CONTENTS

SUMMARY

The intramolecular cyclizations of a number of free-radicals containing the 5-hexenyl system have been investigated.

The radicals were generated via the radical chain reaction between tributylstannane and various alkenyl and cyclo-alkenyl halides, which were synthesized by unambiguous routes. The relative yields of cyclized and uncyclized products were determined by gas liquid chromatography, using authentic compounds as reference specimens. Values of the ratio of the rate constants for cyclization and hydrogen-atom transfer were calculated by computer methods from the integrated rate expression (1), using an iterative procedure.

The salient features of the results obtained are:

(1) 1,5-cyclization is the favoured pathway in the majority of radicals studied containing the 5-hexenyl system.

(2) no evidence was found for concerted cyclization to bicyclic compounds, in radicals containing two suitably disposed olefinic bonds.

(3) the rates of intramolecular cyclization are strongly diminished by alkyl substituents at the olefinic centre of attack.

(4) 6-hepten-2-yl and related radicals undergo cyclization to

form preferentially cis-disubstituted cyclopentane derivatives.

These observations are shown to be consistent with a proposed model for the transition state for radical cyclizations, which is unsymmetrical and comprises a triangular array of centres lying in the same plane as that of the original π bond. Also it is suggested that the regioselectivity exhibited by intermolecular alkyl addition reactions may in fact be due to steric effects, and that the preferential cis cyclization of suitable alkenyl radicals provides an example of orbital symmetry control.

STATEMENT

This thesis contains no material previously submitted for a degree or diploma in any University, and to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference is made in the text.

G. PHILLIPOU.

ACKNOWLEDGEMENTS

I wish to express my appreciation to Professor A.L.J. Beckwith for his encouragement and guidance during the supervision of this work. I would also like to thank the members of the Organic Chemistry Department, in particular Dr. G.E. Gream, Dr. I.A. Blair and G. Moad, who have helped me during my course of study.

My thanks go to my parents who originally made all this possible, and also to my wife, Sophie whose understanding during my study was a great comfort.

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PUBLICATIONS

Part of this work has been published in the following communications:-

A.L.J. Beckwith and G. Phillipou, Chem. Comm., 280 (1973)

A.L.J. Beckwith, I.A. Blair and G. Phillipou, J. Amer. Chem. Soc.,96, 1613 (1974).

CHAPTER 1

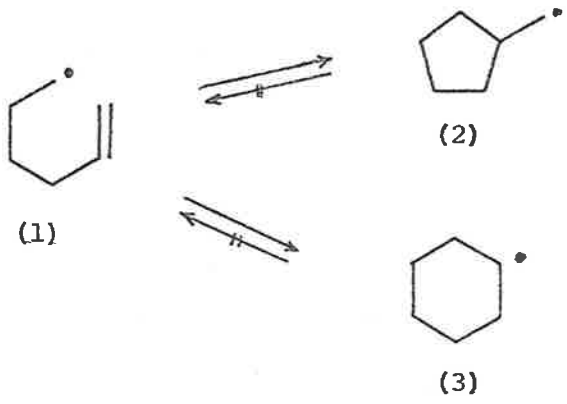
INTRODUCTION

CHAPTER 1

INTRODUCTION

Intermolecular radical additions to double bonds have been extensively studied. However, it has only been in recent times that similar intramolecular processes have received detailed attention.

The simple 5-hexenyl radical (1) generated by a variety of methods[1-9], has been shown to undergo cyclization almost exclusively to the cyclopentylmethyl radical (2). Only traces of products derived from the cyclohexyl radical (3) have been found (Scheme 1).



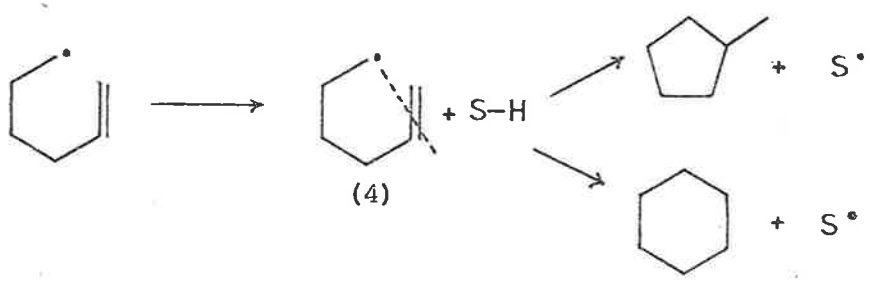
Scheme 1

Importantly, it has been established that the radicals (2) and (3), unless generated at high temperatures in the gas phase[1,2], do not undergo rearrangement[3,6-9].

On first principles the preferential formation of products resulting from the cyclopentylmethyl radical (2) would seem to be unexpected. The cyclohexyl radical (3), being secondary, is expected to be more stable than the primary radical (2). Since in exothermic reactions the rates of reaction are closely related to the thermochemistry, cyclohexyl radical (3) formation would have been predicted.

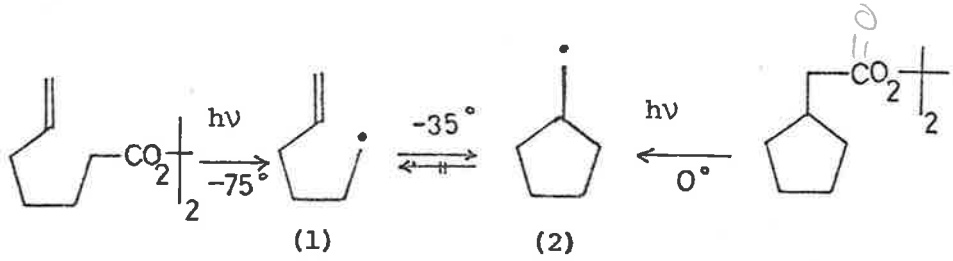
The relative stabilities of the radicals (2) and (3) have in fact been confirmed by the observation that cyclohexaneformyl peroxide decomposes thirty-four times as rapidly as cyclopentylacetyl peroxide[10].

The seemingly anomalous course of the cyclization led several workers[3,8] to suggest that intramolecular complex formation (4) occurred between the free-radical centre and the double bond. The steric requirements in the two transition states leading to 5 and 6-membered ring products were therefore envisaged as determining the direction of the reaction (Scheme 2).



Scheme 2

Kochi and his co-workers[11], investigated the homolytic rearrangements of the 5-hexenyl (1) and cyclopentylmethyl (2) radicals by electron paramagnetic resonance (e.p.r.) spectroscopy (Scheme 3).



Scheme 3

They confirmed that the radical (2) has a discrete existence in the cyclization process and that its formation is indeed irreversible. In a further elegant extension of this work, Kochi and Edge[12] utilized the e.p.r. parameters derived from the spectrum of the 5-hexenyl radical, to deduce that the most stable conformation for the radical requires the unsaturated linkage to lie over the free-radical centre (Fig. 1).

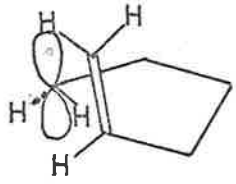


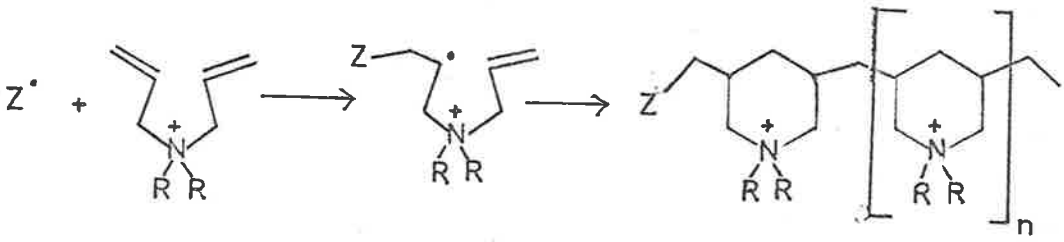
Fig. 1

Kochi, however, was quick to suggest that it is not necessary for a relationship to exist between the stable conformation of a radical and its propensity for cyclization. He cited the case of the 3-butenyl radical (5) where cyclization is known[13], although the radical (5) does not exist in a preferred conformation (Scheme 4).

(5)

Scheme 4

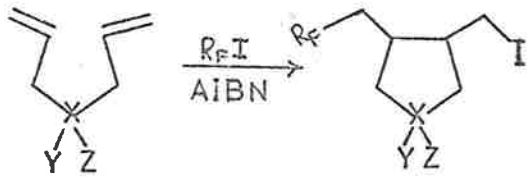
The preceding observations contrasted sharply with early work in cyclopolymerization[14,15], where addition of various radicals to 1,6-diolefins was believed to form polymers containing 6-membered rings as the recurring unit (Scheme 5).



Scheme 5

Related free-radical reactions of 1,6-heptadiene and its analogues with various addenda have also been reported to yield 6-membered ring structures[16].

These initial assignments of 6-membered ring structures to the cyclic adducts, however, were soon challenged. Brace[17], in particular, found that the radical-initiated addition of perfluoroalkyl iodides (R_FI) to various substituted 1,6-heptadienes gave products containing only 5-membered rings (Scheme 6).

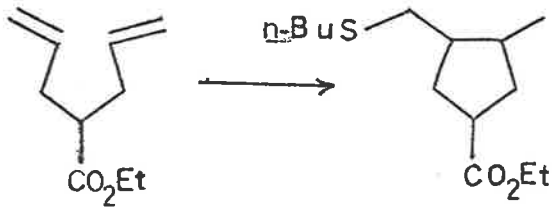


X = C; Y,Z = H or CO_2Et

X = N; Y = H; Z = MeCO, CF_3CO, C_6H_5CO, CH_2CH_2CN, CN

Scheme 6

Cadogan, Hey and their co-workers[18] similarly found that the radical-initiated addition of n-butane-thiol to ethyldiallyl-acetate (6) gave the substituted cyclopentane (7) as the sole cyclic product (Scheme 8)*.



(6) (7)

Scheme 8

In an attempt to get more information about the nature of the transition state for cyclizations of the preceding type. Brace[19] correlated the relative reactivity of terminal alkadienes towards perfluoroalkyl iodides, both as a function of chain length and reaction conditions. The relevant results are shown in Table I.

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* It must be mentioned that, in the preceding examples, acyclic adducts as well as bisadducts were also formed.

Table 1

Relative reactivity per double bond of alkenes and dienes with C_4F_9I

1-hexene	1.03
1-heptene	.996
1,4-pentadiene	.935
1,5-hexadiene	.805
1,6-heptadiene	1.08-1.42[a]
1,7-octadiene	.945

a. dependent on $[C_4F_9I]$

Brace interpreted the enhanced reactivity of 1,6-heptadiene as being related to its ability to cyclize, since the other alkadienes gave no cyclic products. Accordingly, he postulated that an across homoconjugation existed between:

(1) the two double bonds;

(2) the radical centre and the π electrons of the remaining double bond in the intermediate involved in the cyclization.

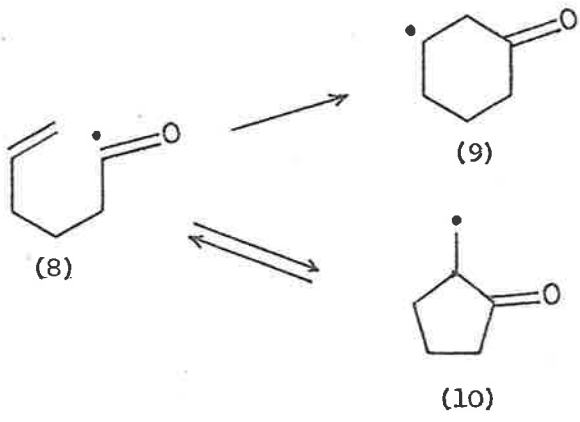
It is suggested that a combination of these two effects may lower the activation energy for the cyclization process[19,20].

An examination of Dreiding models of 1,6-heptadiene indeed shows that a very favourable conformation exists for the across space homoconjugation, which leads to 5-membered ring closure and where a strong π-π interaction of the nodal planes of all p-orbitals

is possible.

Closely related to the preceding examples the intramolecular cyclizations of acyl radicals containing a suitably disposed olefinic moiety has also been observed[21-24]. The unsaturated acyl radicals are generated either by hydrogen-atom abstraction from the aldehyde, or, tributyltin hydride reduction of the acyl chloride[25].

The 5-hexenoyl radical (8) has been shown to cyclize exclusively to the more stable 6-membered ring radical (9)[21,24] (Scheme 9).

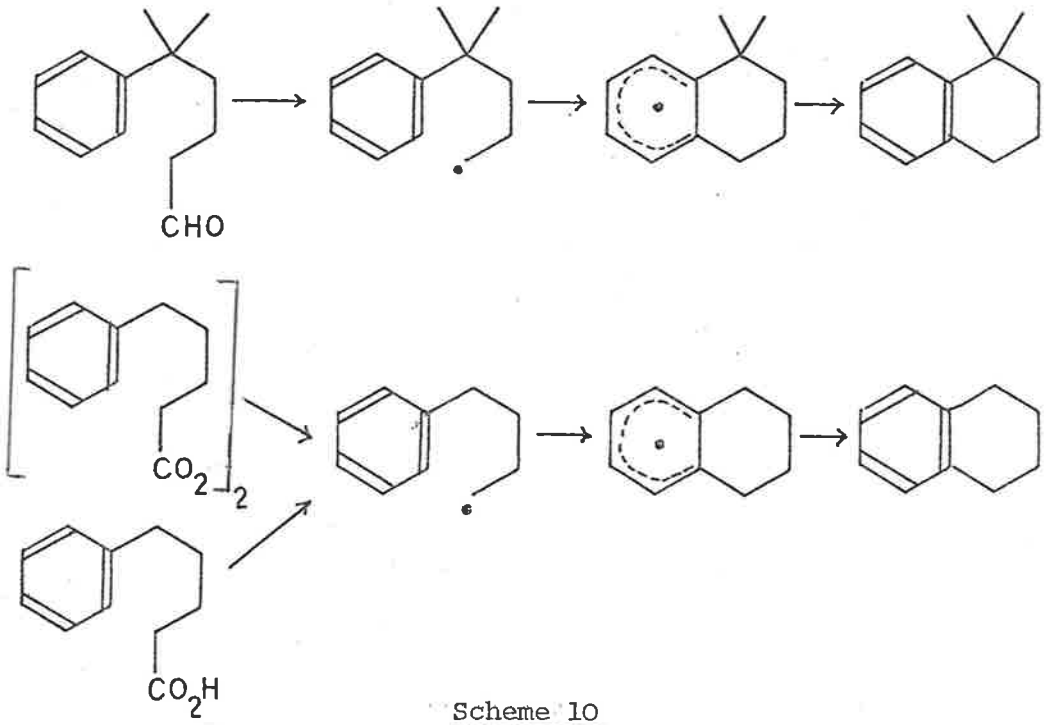


(8) (9) (10)

Scheme 9

The formation of the radical (10), however, has been shown to be reversible[26], which suggests the cyclization of the acyl radical (8) is under thermodynamic control.

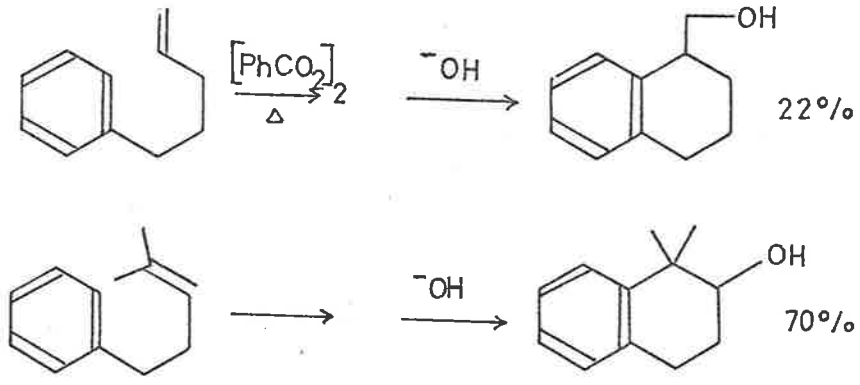
There are also numerous examples in which cyclizations involving aromatic rings take place. 4-Phenylbutyl radicals have been shown to undergo Ar_2-6 cyclization, particularly when the solvent is a poor hydrogen-atom donor. These radicals were derived by decarbonylation of the aldehyde[27], decomposition of the acyl peroxide[28] or electrolysis of the acid[29] (Scheme 10).



Scheme 10

The aromatization step in these cyclizations may occur via disproportionation, oxidation by other radicals present, or by oxidation during work-up of the reaction.

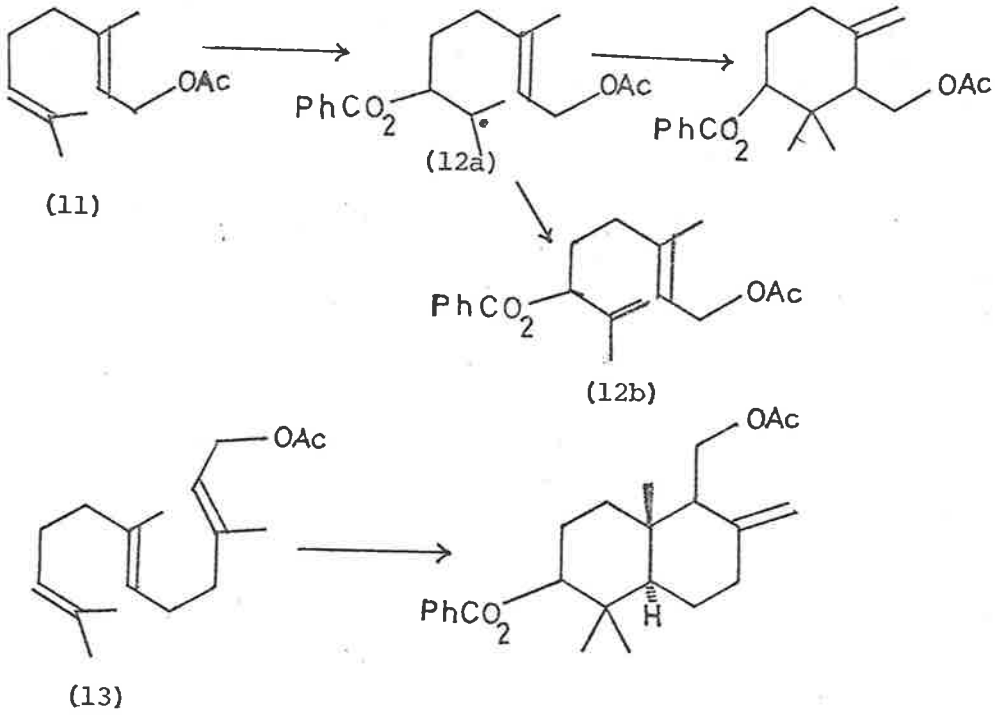
In an extension of this type of cyclization it was found that the ease of acyloxy radical addition across the double bond and the contingent Ar_2-6 rearrangement is related to the substitution of the double bond[30] (Scheme 11).



Scheme 11

Intramolecular radical additions leading to the formation of bi- or polycyclic systems have been less extensively studied.

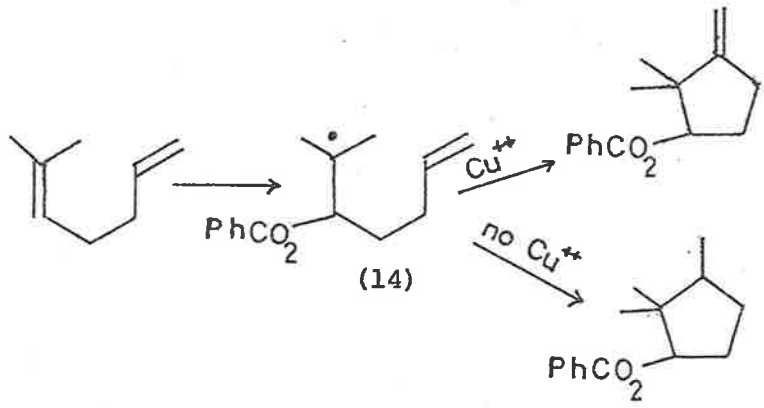
Breslow and his co-workers[31] using benzoyloxy radicals, generated by the cuprous chloride-catalyzed thermal decomposition of benzoyl perioxide, were able to bring about the oxidative cyclization of geranyl (11) and farnesyl (13) acetates in benzene (Scheme 12).



Scheme 12

The amount of acyclic terminal methylene products (12b) derived from the radical (12a) was found to increase with increasing concentration of cupric benzoate indicating the competition between radical oxidation and cyclization.

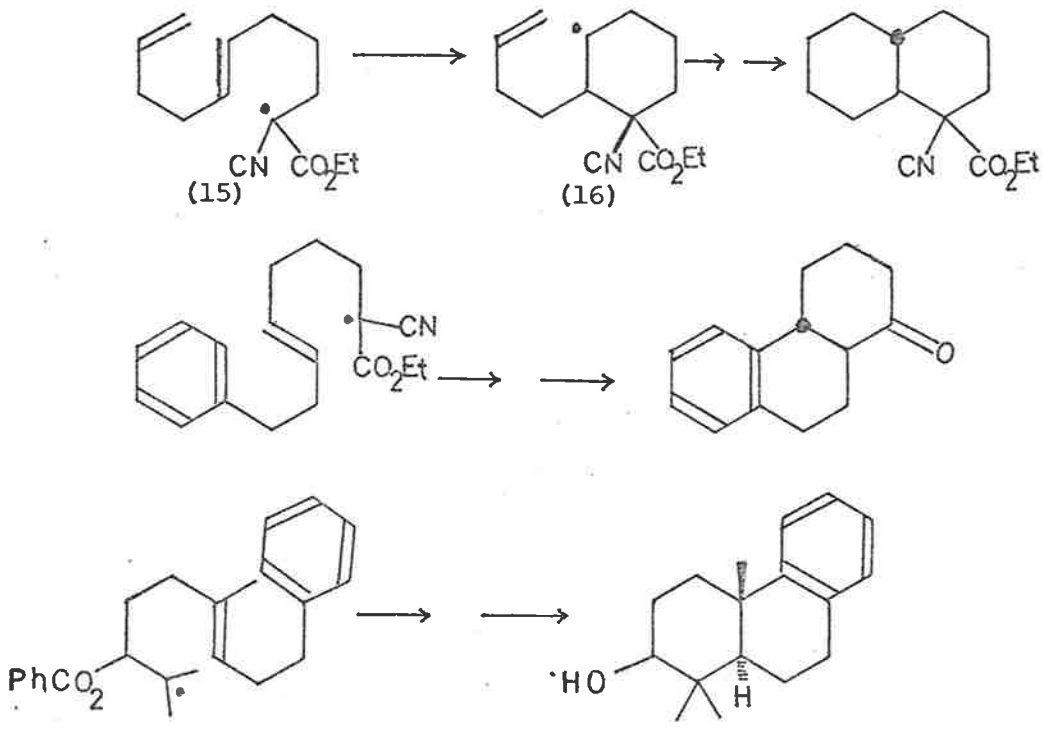
Further evidence for the radical nature of the cyclization pathway (Scheme 12) has been obtained from the copper-ion catalyzed decomposition of bis-5-(1-cyclohexenyl) pentanoyl peroxide[32] and also from the cyclization of the radical (14) in the presence and absence of copper salts[33] (Scheme 13).



Scheme 13

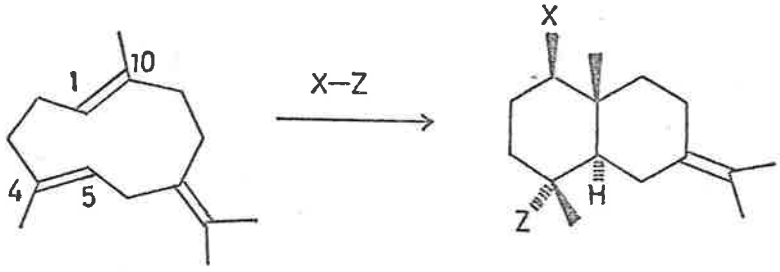
The cationic route to cyclic products derived in the presence of copper, however, cannot be completely discounted.

Other workers[33-35] have investigated radicals which are claimed to cyclize to trans- fused ring structures (Scheme 14).



Scheme 14

The cyclization of germacrene (17) has been reported[36] to be a concerted process leading specifically to a trans-decalin derivative by a synchronous C-X and C_5-C_{10} bond formation (Scheme 15).

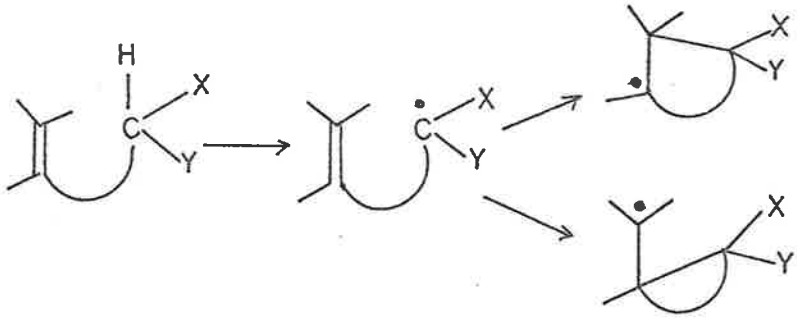


(17) X-Z = PhS-H, PhS-SPh, CCl_3-Cl

Scheme 15

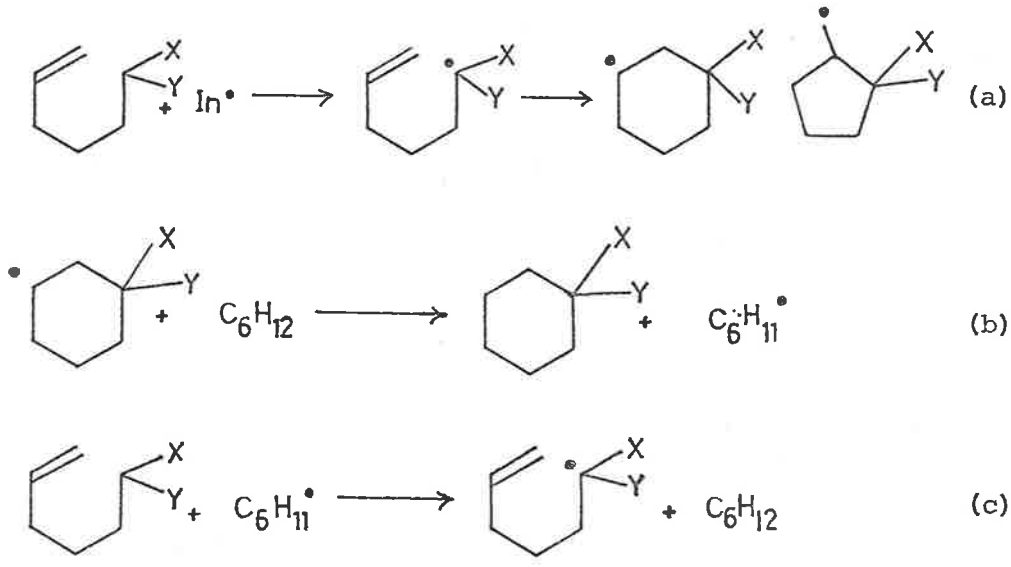
On considering the complexity of the changes effected in one step in the compounds represented in Schemes 12, 14 and 15, it would seem that such reactions should have considerable synthetic utility. Furthermore, the structural preference for 6-membered ring products and the stereochemical selectivity associated with these transformations may be of biochemical significance.

Julia and his collaborators[37] have carried out separate studies on cyclizations represented by the general Scheme 16.



Scheme 16

Maximum cyclization was obtained by conducting the reactions at high dilution in cyclohexane as solvent and using benzoyl peroxide as an initiator. Julia[37b] believes the cyclization reactions to be chain reactions in which the solvent acts as the hydrogen-atom donor (Scheme 17).



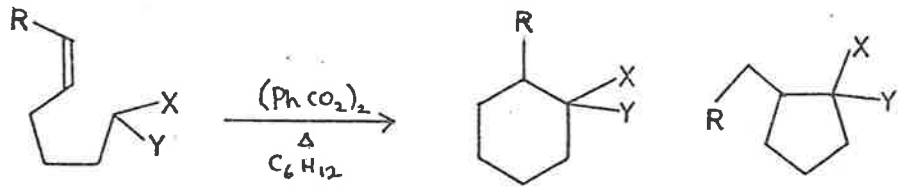
Scheme 17

It has been found, however, that this type of reaction consumes considerable amounts of initiator indicating the absence of long propogating chains.

Some of Julia's pertinent results which are summarized in Table 2, show that 6-membered ring formation increases as the stability of the acyclic radical increases.

Table 2

Cyclization of some substituted 5-Hexenyl radicals

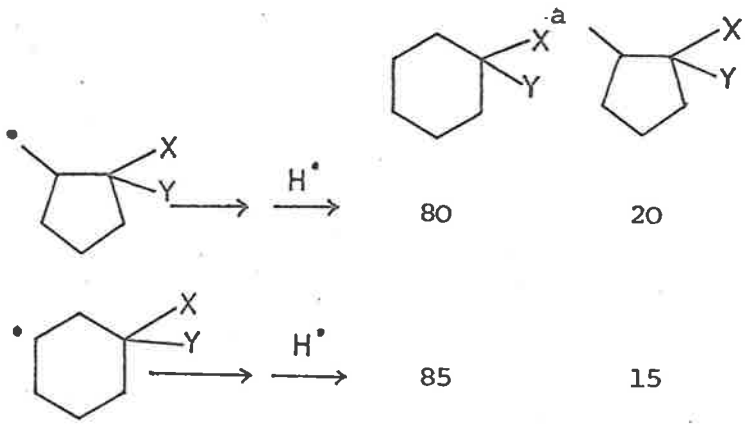


X	Y	R		
H	H	H	0	100
CN	H	H	0	100
$COCH_3$	H	H	28	72
$CO_2C_2H_5$	H	H	44	56
CN	CO_2Et	H	84	16
CN	CO_2Et	Me	100	0

Furthermore, it was established that the acyclic radicals which are stabilized by cyano and carbethoxy groups undergo cyclizations which are reversible[26] (Table 3).

Table 3

Study of reversibility of cyclization process



a X = CN; Y = CO_2Et.

The reversibility of these cyclizations was also shown by conducting the reaction at low temperatures or in the presence of an efficient hydrogen-atom donating solvent. Under these experimental conditions, a much greater proportion of 5-membered ring products ~~were~~ was obtained.

On the basis of his experimental observations, Julia made the following conclusions concerning radical cyclizations;

(i) When the cyclization is under kinetic control, 5-membered ring products are favoured.

(ii) When the cyclization is reversible and therefore under thermodynamic control, 6-membered ring products are favoured. Thermodynamic control may be achieved in the following ways:

(a) high reaction temperature;

(b) functional groups which stabilize the acyclic radical;

(c) poor hydrogen-atom donating ability of the reaction medium.

In an attempt to explain the kinetic preference for 1,5-cyclization, Julia[26,33] suggested that the 1,6-cyclization of the 5-hexenyl radical and related species is hindered by a non-bonded interaction between the pseudo-axial hydrogen at C_2 and the substituent at C_6[26] (Fig. 2).

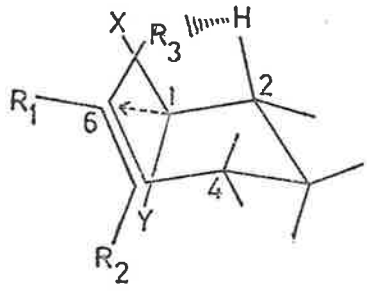
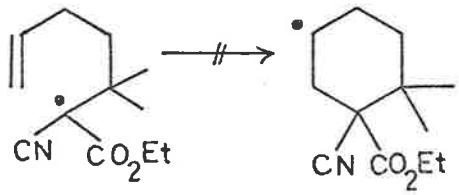


Fig. 2

Models of the transition state, however, which allow for a C_1-C_6 distance greater than the C-C bond length, and for a change towards sp^3 hybridization at C_6, do not reveal any such severe interactions.

As justification of his proposals, Julia[33] states that the C_2 dimethylated radical (18) does not undergo cyclization (Scheme 18).



(18)

Scheme 18

This statement is difficult to reconcile with his original suggestion that the radical (18) could not form due to the steric hindrance to removal of the hydrogen atom[37a,38].

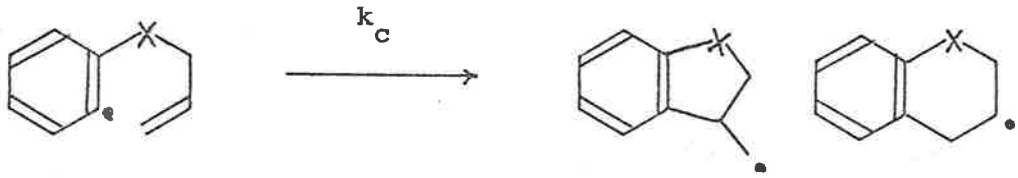
In recent years, Beckwith and his co-workers have attempted to delineate the factors affecting the direction of radical cyclization. The approach, a systematic study of the reactions of various alkenyl halides with tributylstannane, was originally developed by

Walling[8]*.

In particular, Beckwith and Gara[40] investigated the intramolecular addition of aryl radicals to suitably disposed double bonds (Table 4).

Table 4

Cyclization of alkenyl aryl radicals



X	$k_c \times 10^{-5}$ a		
$-CH_2-$	5.4	>99	< 1
-NMe-	31	100	0
-O-	630	100	0

a. rate constant for overall cyclization (sec^{-1}).

The cyclization reactions summarized in Table 4 proceed exclusively by 1,5-intramolecular addition. The rate of cycliza-

* Kuivila and Menapace[39], however, were the first to report that halides could be converted to their respective hydrocarbons with this reagent.

tion was shown to be dependent on the nature of the element at the 1-position in the 3-butenyl side chain. It has been suggested that the rate may be the result of a decrease in the distance between the free-radical centre and the position at which cyclization occurs in the side-chain.

In an earlier report, Beckwith[41] stated that the transition state for homolytic addition to a π system has stereochemical requirements which, because of the constraints of ring size, cannot be attained in many cyclization reactions.

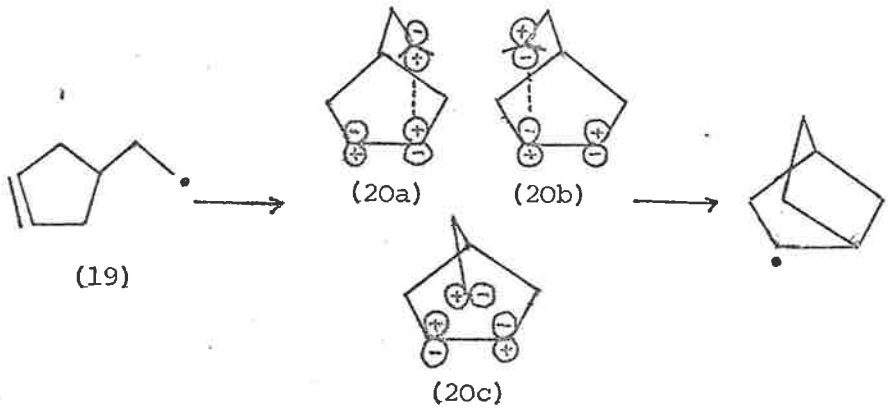
Examination of models led to the suggestion that bond formation in radical addition reactions requires approach of the radical centre within the plane of the π orbital and along an axis extending vertically from one of the terminal atoms.

This hypothesis was then further developed to include the concept of a requirement for maximum overlap between the half-filled p-orbital and the vacant π^* orbital[42].

Although this model for the transition state in homolytic addition reactions rationalizes the preferential formation of cyclopentylcarbinyl radicals from acyclic species, it does not account satisfactorily for the cyclizations in the alkenyl aryl radicals. In this instance, cyclization leading to 6-membered rings seems to be favoured when p-π^* interactions are considered; however,

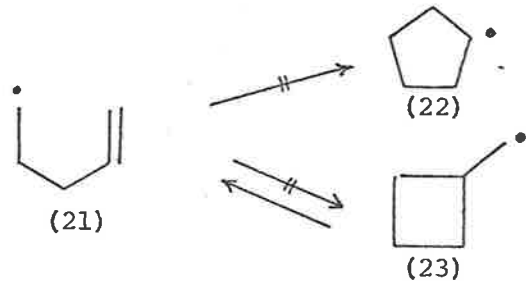
only 1,5-cyclization is observed. It therefore becomes obvious that there are additional factors which must be delineated before a true representation of the transition state may be obtained.

Wilt and his co-workers[43] have studied the cyclization of 2-(cyclopent-3'-enyl) ethyl radical (19). To account for the formation of the 2-norbornyl radical in this reaction, they postulated a symmetrical transition state (20c) based on the p-π* orbital overlap theory. Examination of Dreiding models, however, indicates that conformational factors may hinder the attainment of the transition state (20c) and it may be better represented by (20a) or (20b) (Scheme 19).



Scheme 19

Finally, it should be noted that the 4-pentenyl radical (21) does not cyclize[4,5,8,44] whilst formation of the cyclobutylmethyl radical (23) is a strongly endothermic process (Scheme 20).



Scheme 20

Although, initially, this observation could not be adequately rationalized, the p-π* orbital overlap theory now provides an explanation. It becomes obvious from a study of models that the orbital interactions leading to the cyclopentyl radical (22) from the acyclic radical (21), cannot be attained.

OBJECTIVES

From the Introduction, it is clear many aspects concerning the direction of intramolecular free-radical cyclizations cannot be adequately rationalized by the theories that have been advanced.

In order that the factors involved in radical cyclizations may be more precisely delineated, it is obvious that the following investigations are warranted:

(1) a more detailed study of alkyl substituent effects, than that previously undertaken[33];

(2) the stereochemistry of the reaction;

(3) the complete description of the transition state for these processes.

With these objectives in mind, detailed product and rate studies were undertaken for a series of substituted 5-hexenyl radicals, such that each particular radical considered elucidated some further details of the mechanism.

CHAPTER 2

EXPERIMENTAL METHODS

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EXPERIMENTAL METHODS

Kuivila and his co-workers[39,45] have established that the reduction of an alkyl halide with a trialkyl- or triaryl-stannane, proceeds by a free-radical chain reaction (Scheme 21).

INITIATION

$$\text{Initiator} \rightarrow R^{\bullet}$$

PROPOGATION

$$R^{\bullet} + R_3'SnH \rightarrow RH + R_3'Sn^{\bullet}$$

$$RX + R_3'Sn^{\bullet} \rightarrow R^{\bullet} + R_3'SnX$$

TERMINATION

$$\left.\begin{array}{l} R^{\bullet} + R^{\bullet} \rightarrow \\ R^{\bullet} + R_3'Sn^{\bullet} \rightarrow \\ R_3'Sn^{\bullet} + R_3'Sn^{\bullet} \rightarrow \end{array}\right\} \text{inactive products}$$

Scheme 21

Furthermore, they showed by a series of competitive experiments that the relative reactivities of alkyl halides towards tri-n-butyltin radicals increased in the order F < Cl < Br < I, whilst for any individual halide the series primary < secondary < tertiary was obeyed.

Subsequently, Carlsson and Ingold[46] investigated the detailed kinetics of these reductions and unequivocally confirmed the two-step free-radical mechanism.

The following salient points emerge from their work;

(i) The rate usually shows first-order dependence on either the alkyl halide or the stannane concentration.

(ii) The reactions behave normally throughout their entire course, continuing until one of the reactants is completely consumed.

(iii) For reactions of alkyl bromides and methyl iodide, chain termination occurs by self-reaction of two alkyl radicals; the rate controlling step is hydrogen-atom abstraction from the stannane.

(iv) For the reduction of alkyl chlorides chain termination involves the coupling of two stannyl radicals; the rate controlling step is chlorine atom abstraction from the alkyl chloride.

(v) The rates of hydrogen-atom abstraction by alkyl radicals from tri-n-butylstannane show only a marginal dependence on the nature of the alkyl radical. The calculated values are summarized in Table 5.

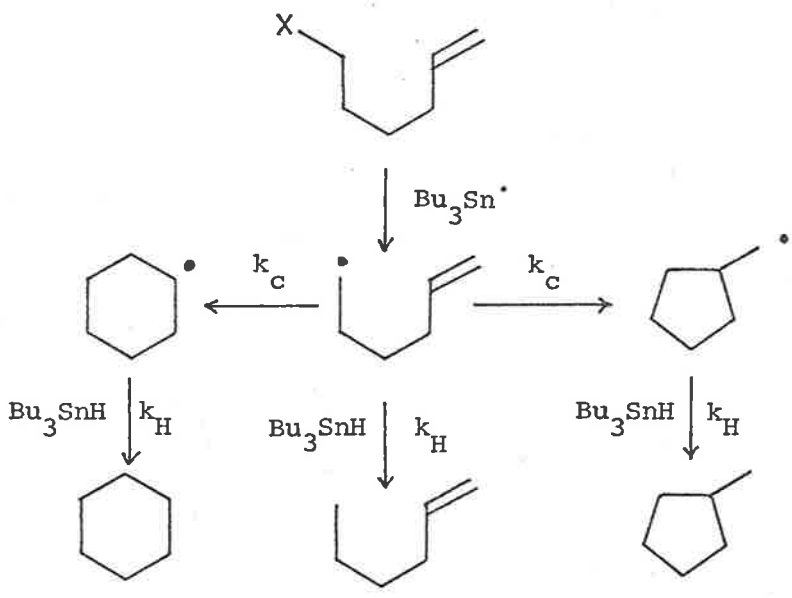
Table 5

Hydrogen-atom abstraction from tri-n-butylstanne

$$R^{\cdot} + \underline{n}\text{-}Bu_3SnH \xrightarrow{k_H} R\text{-}H + \underline{n}\text{-}Bu_3Sn^{\cdot}$$

	$k_H \times 10^{-6}$ sec^{-1}
$(Me)_3C^{\cdot}$	.74
$CH_3(CH_2)_4\text{-}CH_2^{\cdot}$	1.0
$S\text{-}C_6H_{11}^{\cdot}$	1.2
$CH_3^{\cdot}$	.58

The estimation of the absolute rate constants for hydrogen-atom transfer from tri-n-butyltin radicals to alkyl radicals are of considerable significance, for such reactions may be used as standards against which the rates of intramolecular processes involving the alkyl radicals may be measured. Consider the reaction sequence (Scheme 22) for the cyclization of the simple 5-hexenyl radical.



Scheme 22

If we assume that the reduction is a long-chain process and that the cyclization steps are irreversible, application of steady state principles allows derivation of the integrated rate expression (equation (1)), which may be solved by computer methods, using an iterative procedure.

$$[C] = \ln \frac{[S]_o + r}{[S]_f + r} \; r \qquad (1)$$

where [C] = concentration of cyclized products formed via a first order process.

r = rate of cyclization relative to the rate of hydrogen-atom transfer from stannane

$$\text{i.e.} = \Sigma k_C/k_H \ .$$

$[S]_{o,f}$ = initial and final concentrations of stannane respectively.

The experimental procedure is as follows:

The reactants, for which the concentrations are accurately known, are heated in a suitable solvent containing a trace of azobisisobutyronitrile (AIBN) as initiator. The experiments afford tributyltin halides as the sole involatile products and consequently the reaction mixtures may be directly analyzed by gas liquid chromatography (g.l.c.). From such studies the product distributions and kinetic parameters, which are subsequently discussed in this thesis were calculated. For clarity and convenience certain aspects warrant comment at this stage.

The experiments were conducted over at least a four-fold range of stannane concentration. Accordingly, since the rate of cyclization is dependent on the stannane concentration, a change in this factor should be reflected in a change in the yield of cyclized products. In cases where this relationship was not observed, it was probable that the cyclized product was formed by mechanisms other than those of a radical nature. Where there is more than one mode of cyclization, however, the yields of cyclized products must be in a constant ratio, which is independent of the stannane concentration.

If this latter condition is not obeyed, or if the cyclization reactions are reversible, the kinetic scheme will not be valid, and the application of equation (1) will not give consistent values. The product distributions were also found to be independent of which reactant was in excess or whether benzene or n-pentane was used as solvent.

Since trialkylstannanes are known to add reversibly to double bonds[47], an experiment was undertaken in which 1-heptene and trans-2-heptene were allowed to react with stannane in the presence of AIBN. After 24 hr, both olefins were recovered in quantitative yield.

The irreversibility of the cyclization process, when stannane is the active hydrogen-atom donor has been established in numerous cases[8,41,48-50].

A number of authentic compounds were required for comparison with products from the free-radical reactions. In most cases, their preparation is described in the Experimental section.

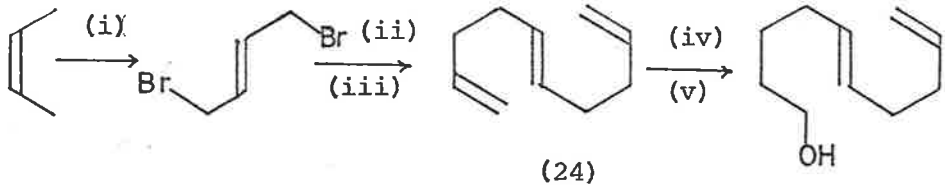
CHAPTER 3

THE DECA-5,9-DIENYL RADICAL

CHAPTER 3

THE DECA-5,9-DIENYL RADICAL

trans-Deca-5,9-dien-1-ol (25) was synthesized by the route outlined in Scheme 23; the configuration of (25) was established by using 1,4-dibromo-trans-but-2-ene as starting material.

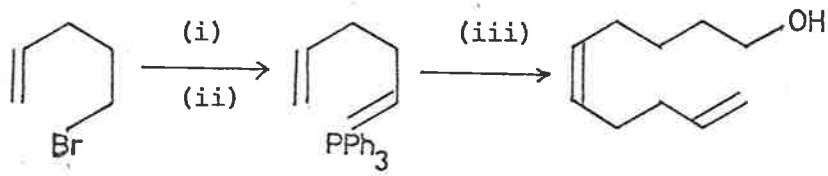


(24) (25)

(i) $Br_2/CHCl_3$ (ii) Mg/Et_2O (iii) $CH_2=CHCH_2Br$ (iv) R_2BH (v) $H_2O_2/^-OH$

Scheme 23

The Wittig reaction between the unstabilized ylid (26) and 5-hydroxypentan-1-al gave a mixture of stereoisomeric alcohols in which the cis isomer (27) clearly predominated to the extent of > 94% (Scheme 24).



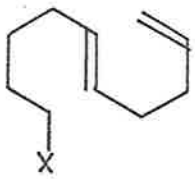
(26) (27)

(i) $Ph_3P/MeNO_2$ (ii) $KOBu^t/Et_2O$ (iii) $HO(CH_2)_4CHO$

Scheme 24

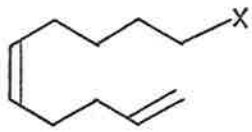
The very high yield of the cis isomer (27) is not unusual for this type of reaction, where the irreversible formation of the erythro betaine is greatly favoured over that ~~for~~ of the threo[51].

Preparation of the trans and cis bromides (28) and (29) was accomplished by converting the alcohols (25) and (27) into their respective p-toluenesulphonates which were then treated with pyridinium bromide in dimethyformamide[52].



(28) X = Br

(30) X = Cl



(29) X = Br

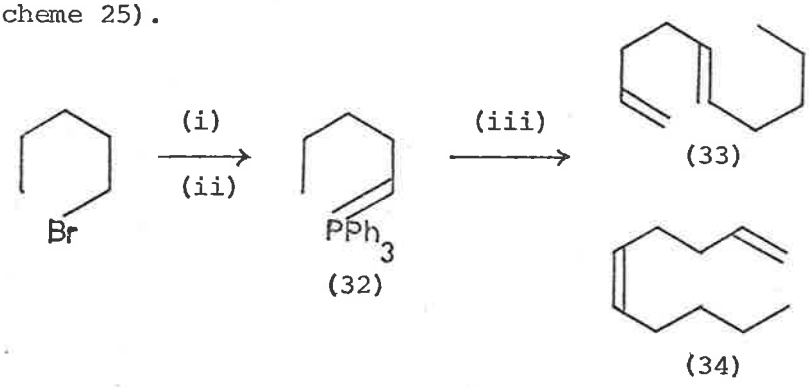
(31) X = Cl

A difficulty encountered with this procedure, however, was that the final bromides (28) and (29) were contaminated with traces of their respective chlorides (30) and (31), formed at the tosylation stage. Since purification of the p-toluene sulphonate (where it could be achieved) would lower the overall yield, it was subsequently decided to form the chlorides in preference to the bromides.

This excellent procedure for the formation of halides is generally restricted to primary systems, since secondary p-toluene-sulphonates tend to undergo elimination reactions.

The Wittig reaction between pentanal and the ylid (32) gave

a mixture of geometric isomers, in which for the reasons given previously, the cis isomer (34) is expected to predominate (Scheme 25).



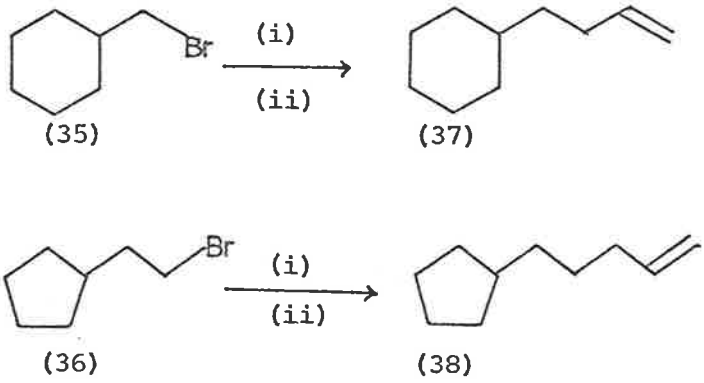
(i) Ph_3P/CH_3NO_2 (ii) $KOBu^t/Et_2O$ (iii) $CH_3(CH_2)_3CHO$

Scheme 25

The exact composition of the mixture could not be determined as the two dienes (33) and (34) were not resolvable by g.l.c. It is noteworthy that the g.l.c. resolution of the isomeric alcohols (25) and (27) was also difficult and required the use of a very specific liquid phase.

Kochi and Tamura[53] have shown that Grignard reagents and alkyl bromides can be effectively cross-coupled in tetrahydrofuran solutions at 0^o when a copper (I) catalyst is used.

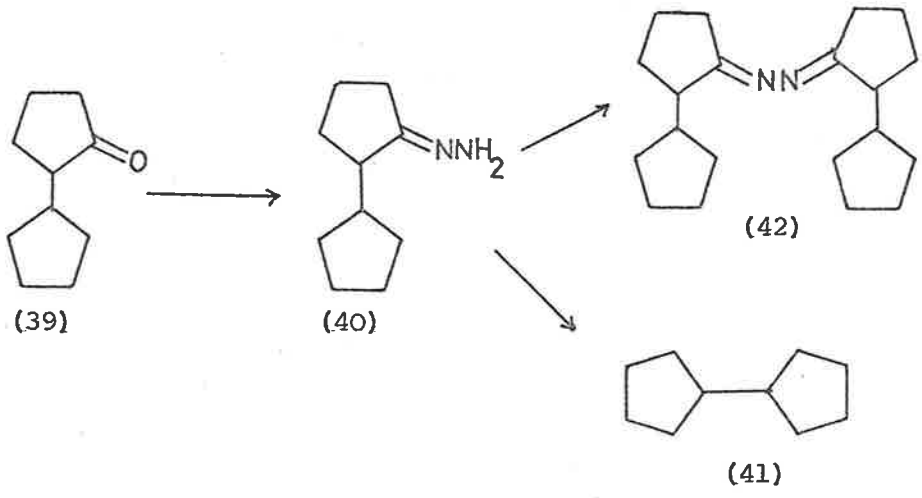
Utilizing a slight variation of this procedure the Grignard reagents of the bromides (35) and (36) were cross-coupled with ~~alkyl~~ allyl bromide to yield specifically and in high yield but-3-enylcyclohexane (37) and pent-4-enylcyclopentane (38) respectively (Scheme 26).



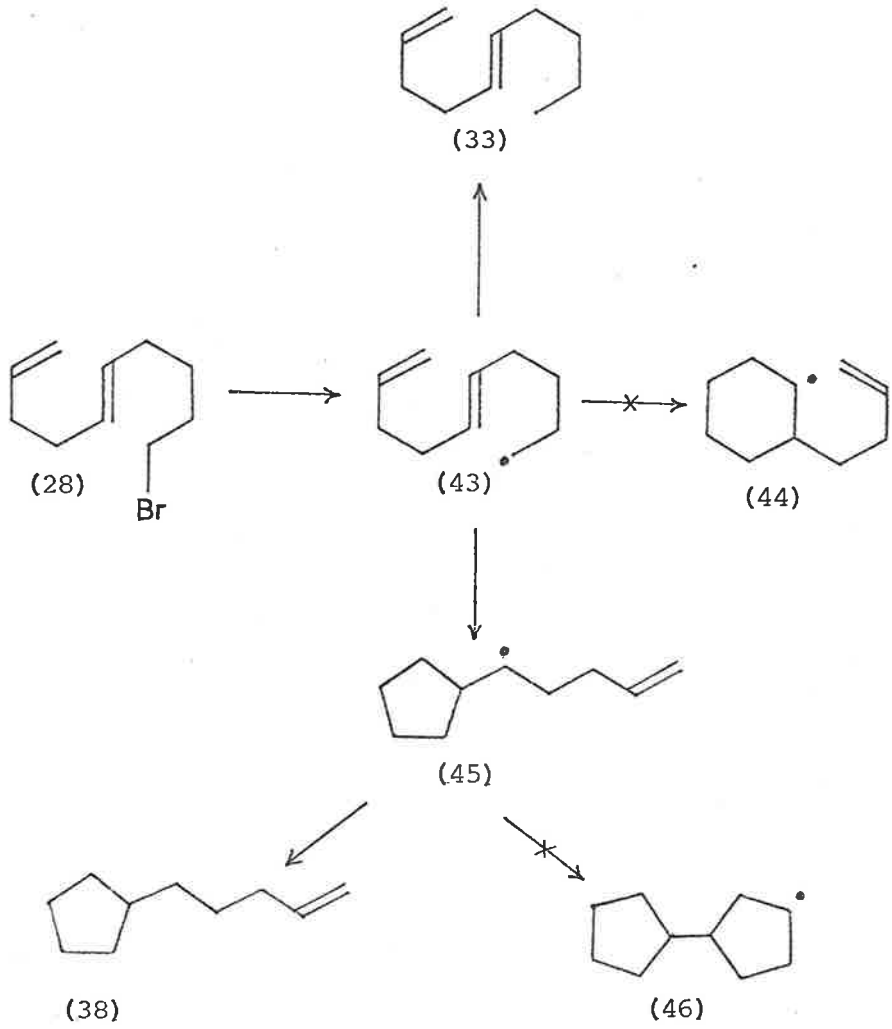
(i) Mg/THF (ii) $CH_2=CHCH_2Br/Li_2CuCl_4/0^o$

Scheme 26

Cyclopentylcyclopentane (41) was conveniently prepared by the Wolf-Kishner reduction of the ketone (39); a byproduct (25%) was the azine (42) formed by condensation of the initial hydrazone (40) with another mole of ketone (39) (Scheme 27).



Scheme 27



Scheme 28

Table 6

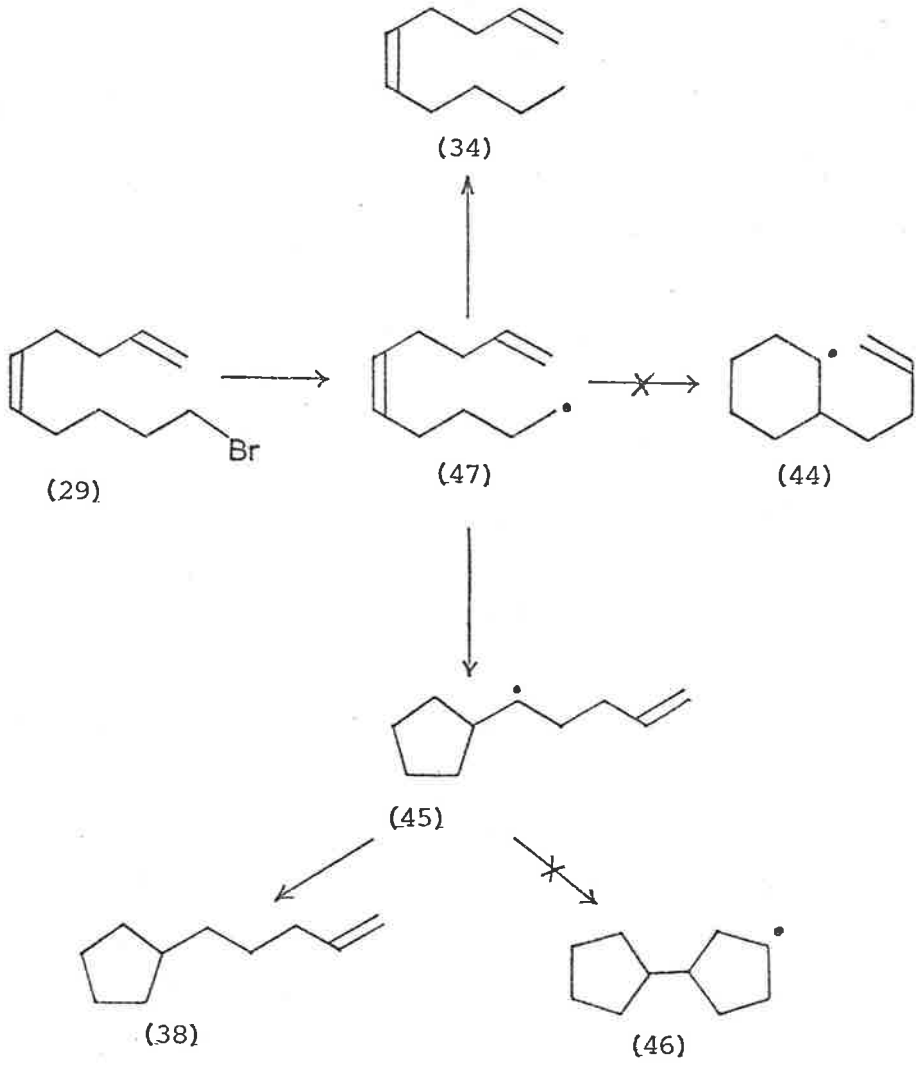
Yields of products from reduction of trans-10-Bromodeca-1,5-diene (28) with Tributylstannane in Benzene

TEMP (°C)	65	65	65	35	75	101
$[Bu_3SnH]_o$ [a]	.078	.191	.556	.662	.662	.662
trans-1,5-decadiene (33)	8.1[c]	19.5	40.1	53.5	39.6	34.8
pent-4-enylcyclopentane (38)	91.9	80.5	59.9	46.5	60.4	65.2
Total yield (%)[b]	77	80	82	87	83	86

a. initial stannane (throughout text).

b. percentage of theoretical based on starting material (refers to stannane unless otherwise stated).

c. relative yield (throughout text).



Scheme 29

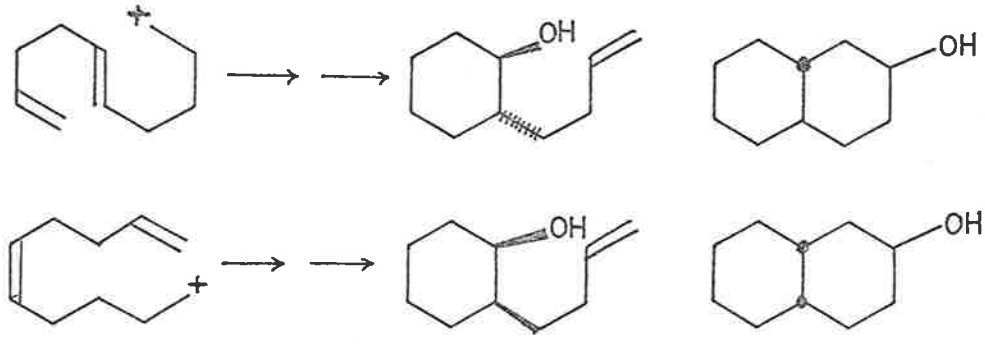
Table 7

Yields of Products from reduction (65°) of cis-10-Bromodeca-1,5-diene (29) with Tributylstannane in Benzene.

$[Bu_3SnH]_o$	.093	.195	.620
cis-1,5-decadiene (34)	11.6	22.9	49.9
pent-4-enylcyclopentane (38)	88.4	77.1	50.1
Total yield (%)	74	82	78

From the data given in Tables 6 and 7, it is seen that the dienyl radicals (43) and (47) exhibit similar behaviour to that of simple acyclic alkenyl radicals[33,42,50]. Cyclization occurs exclusively in the 1,5- direction; unlike the 5-hexenyl radical, however, it should be noted that no detectable traces of 6-membered ring products are observed. The 1-cyclopentylpent-4-enyl radical (45) like its acyclic analogue[4,5,8,44], does not undergo intramolecular addition even at very low concentrations of tributylstannane (< .004M).

These results are in marked contrast to those obtained from the corresponding carbonium ion precursors; in the latter case only 6-membered mono and bicyclic products are formed[54,55] (Scheme 30).



Scheme 30

It has been suggested[55] that there is no common intermediate for the cyclizations of the respective dienyl cations, and the mechanism is postulated to involve either a concerted process or one

where the cationic intermediates retain the stereochemical integrity of their respective substrates.

It is therefore obvious that the transition state leading to cyclized products in carbonium ion precursors bears no resemblance to that observed in corresponding free-radical species. Furthermore, the triangular(bridged) arrangement of groups in the transition state so often invoked in carbonium ion chemistry, is forbidden for free-radical cyclizations by molecular-orbital theory.

It has been reported[34] that the dienyl radical (15) (Scheme 14) cyclizes to yield trans-decalin derivatives*. In the light of the present results, such behaviour must be due to special substituent effects in the particular substrate used, and does not represent an example of a process of wide generality.

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* There is some ambiguity in these assignments due to the very low yield and the number of degradation steps necessary for product identification.

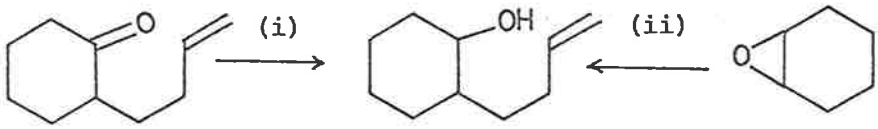
CHAPTER 4

6-HEPTEN-2-YL AND RELATED RADICALS

CHAPTER 4

6-HEPTEN-2-YL AND RELATED RADICALS

2-(But-3'-enyl) cyclohexanol (50) was prepared by ~~either by~~ two methods (Scheme 31). Reduction of the ketone (48) gave a mixture of isomers in which the trans predominated, whilst opening the epoxide (49) gave exclusively the trans isomer.



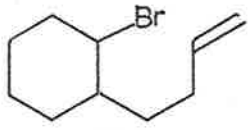
(48) (50) (49)

(i) $LiAlH_4/Et_2O$ (ii) $CH_2=CH(CH_2)_2MgBr/Et_2O$/dioxan

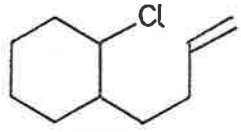
Scheme 31

Experiments in which the alcohol (50) was allowed to react with triphenylphosphine dibromide in dimethyl formamide[56] or with phosphorus tribromide and pyridine in ether[57], both failed to yield pure bromide (51). The attempted displacement of the p-toluene sulphonate was also unsuccessful.

Further experiments directed towards the conversion of the alcohol (50) into the chloride (52), in which triphenylphosphine in carbon tetrachloride[58] or thionyl chloride and pyridine in ether[59] were used, again proved unsatisfactory.



(51)

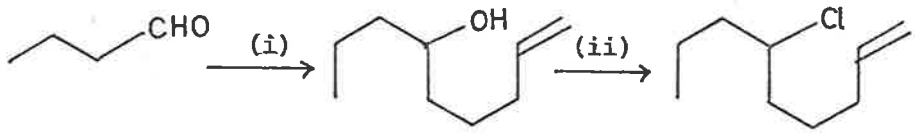


(52)

At this stage it was brought to our attention[60] that phosphorus pentachloride had been successfully used to carry out transformations of alcohols to chlorides.

As a result of a study of various reaction conditions it was found that the chloride (52) could be obtained in high yield and purity, when the alcohol (50) was added at low temperatures to phosphorus pentachloride. The most suitable solvents were chloroform, methylene dichloride and n-pentane. This method, therefore, constitutes an excellent procedure for the preparation of secondary and tertiary halides which are prone to undergo elimination or rearrangement.

6-Chlorohept-1-ene (53) is known[61], whilst 6-chlorononon-1-ene (55) was prepared as shown in Scheme 32.

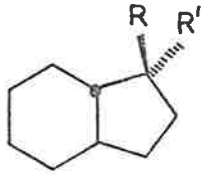


(54) (55)

(i) $CH_2=CH(CH_2)_3MgBr/Et_2O$ (ii) $PCl_5/CHCl_3$

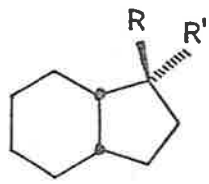
Scheme 32

The stereochemical assignments of the four isomers of 1-methyl-bicyclo [4.3.0] nonane, (56), (57), (58) and (59) were derived in the following manner.



(56) R=Me,R'=H

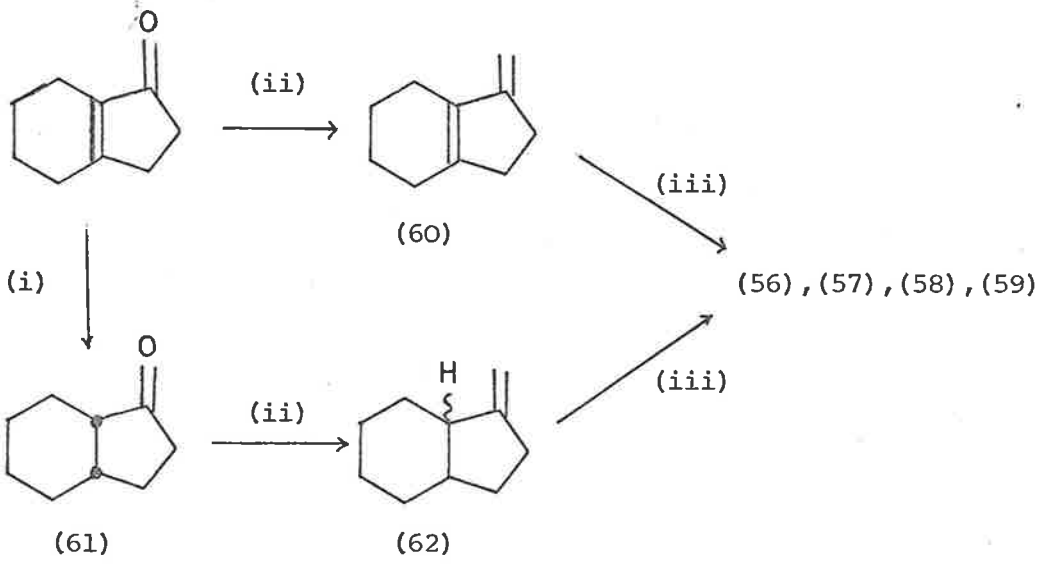
(57) R=H, R'=Me



(58) R = Me, R'=H

(59) R = H, R' = Me

The diene (60) and the olefin (62) were prepared and converted to the hydrocarbons (56)-(59) as shown in Scheme 33.



(i) $Pd/H_2/MeOH$ (ii) $Ph_3P=CH_2/Et_2O$ (iii) $PtO_2/H_2/Et_2O$

Scheme 33

The olefin (62) was shown by g.l.c. to be a mixture of isomers in which the trans compound is tentatively identified as the major constituent on the basis of its g.l.c. parameters. The starting ketone (61) is solely the cis isomer, therefore the preferential formation of the trans olefin (62) indicates that epimerization of the ketone (61) must occur under the reaction conditions.[129]

It is of interest to compare the hydrocarbon mixtures obtained by hydrogenation of (60) and (62) with similar studies[62] for the compound (63) (Table 8). The stereochemistry of the four

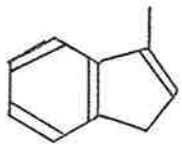
isomers (56)-(59) formed from (63) was assigned on the basis of:

(i) cis hydrogen from the less hindered side; and

(ii) stability of the isomers in the presence of various catalysts.

Table 8

Yield of products (56)-(59) from hydrogenation of various precursors

precursor	$\xrightarrow{H_2}$	(56)	(57)	(58)	(59)
 (60)		4.4	6.5	23.7	62.5
(63)		3.7	10.3	30.0	56.0
(62)		17.6	34.6	7.2	40.6

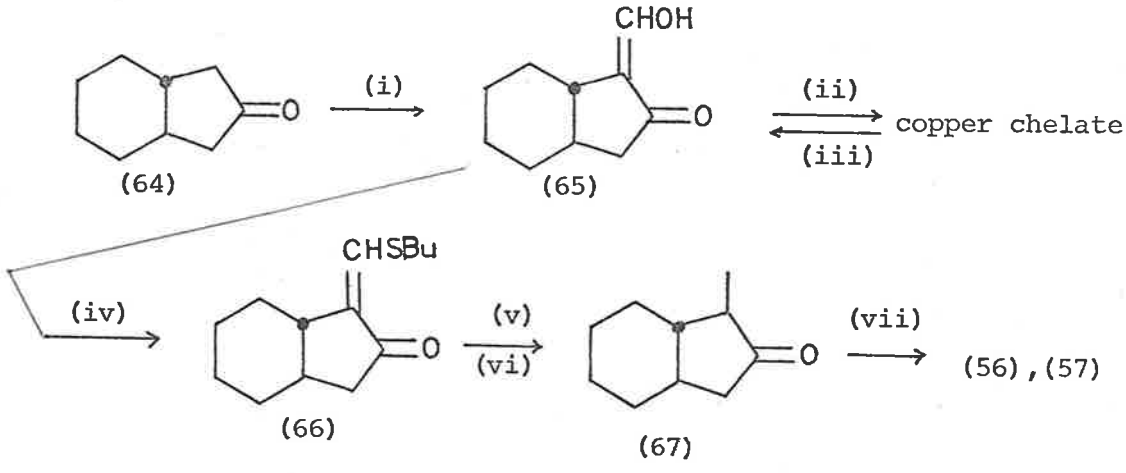
From the Table 8, it can be seen that the compounds (60) and (63) give very similar isomer distributions, favouring the formation of those isomers (58) and (59) possessing a cis fused ring junction.

The two isomers in the mixture of the olefin (62), for which the stereochemistry at the ring junction is defined prior to hydrogenation, are ~~seem~~ seen to yield a greater proportion of those isomers (56) and (57) which possess a trans ring junction.

As further corroborative evidence, the isomers (58) and (59) whose stereochemistry was assigned on the basis of the preceding hydrogenation studies, had identical g.l.c. characteristics with

those of authentic samples, in which the ring junction stereochemistry had been unequivocally estalished[63].

To complete the assignment, the two isomers (56) and (57), possessing a trans ring junction, were synthesized by an unequivocal route (Scheme 34).



(i) NaH/HCO_2Et (ii) $Cu(OAc)_2/MeOH$ (iii) H_2SO_4/Et_2O

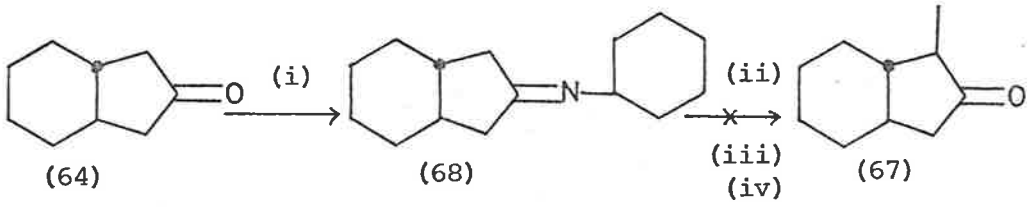
(iv) n-BuSH/benzene (v) Ra-Ni/EtOH (vi) [O] (vii) Zn/Hg/conc HCl

Scheme 34

The desulphurization of the compound (66) gave a mixture of alcohols and ketones which were oxidized to yield the ketone (67) as a mixture of epimers. The final ratio of the two isomers (56) and (57) was ca. 98:2, which is in agreement with the report[62] that the hydrocarbon (56) is thermodynamically the more stable of the two

isomers.

The above route, however, is lengthy and therefore an alternate route was investigated; it failed however to give the ketone (67) which was the key intermediate (Scheme 35).



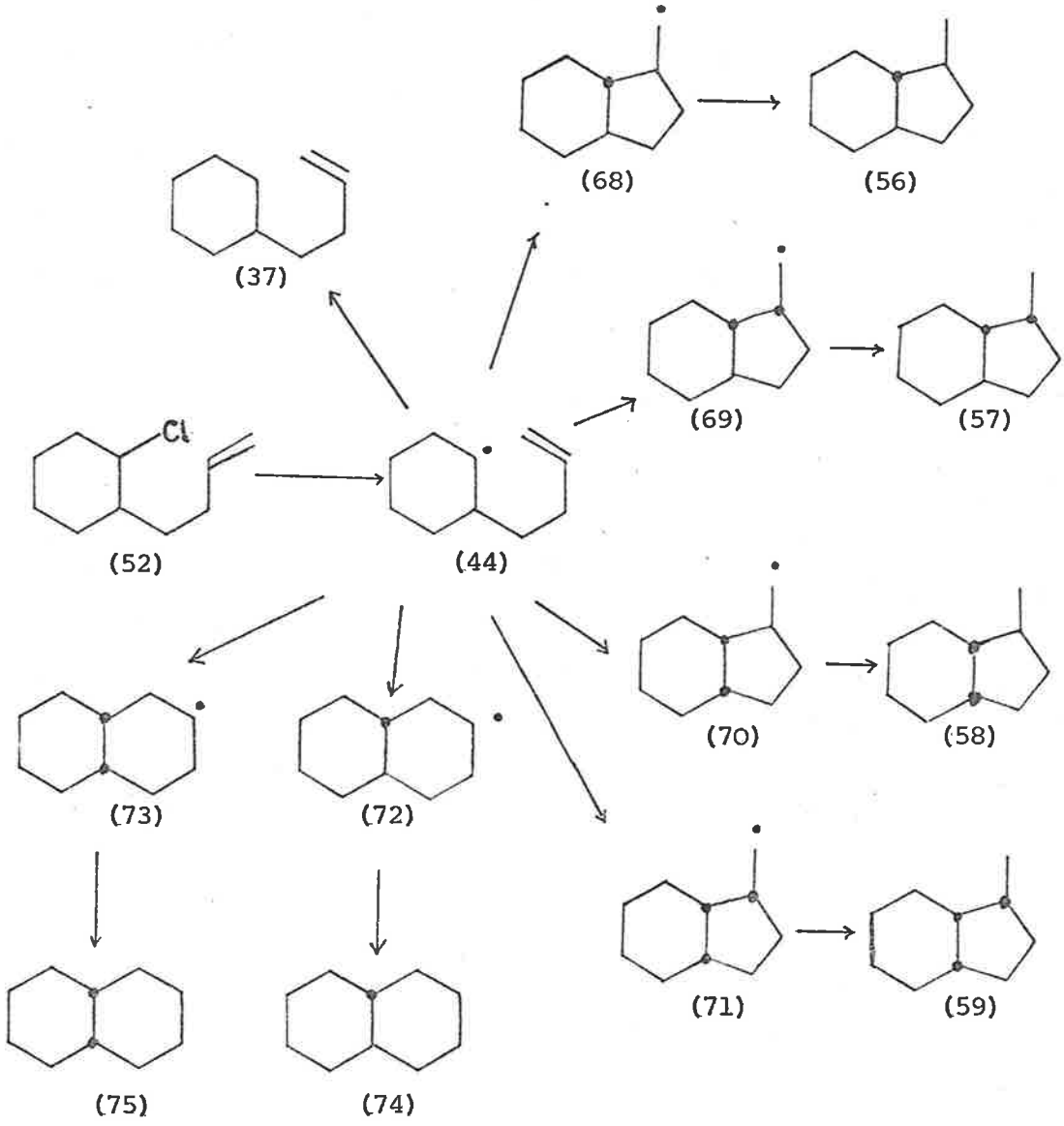
(64) (68) (67)

(i) $NH_2C_6H_{11}$/benzene (ii) MeMgI/THF (iii) MeI (iv) H^+

Scheme 35

The transformation (68) → (67) had been used previously to prepare the ketone (48) in high yield.[89]

Although the assignments of configuration at the ring junctions in the four isomers hydrocarbons (56)-(59) are unequivocal, there is some doubt about the assignments at the other isomeric centre. The conclusions however reached in the present work are in accord with those previously reported[62,63].



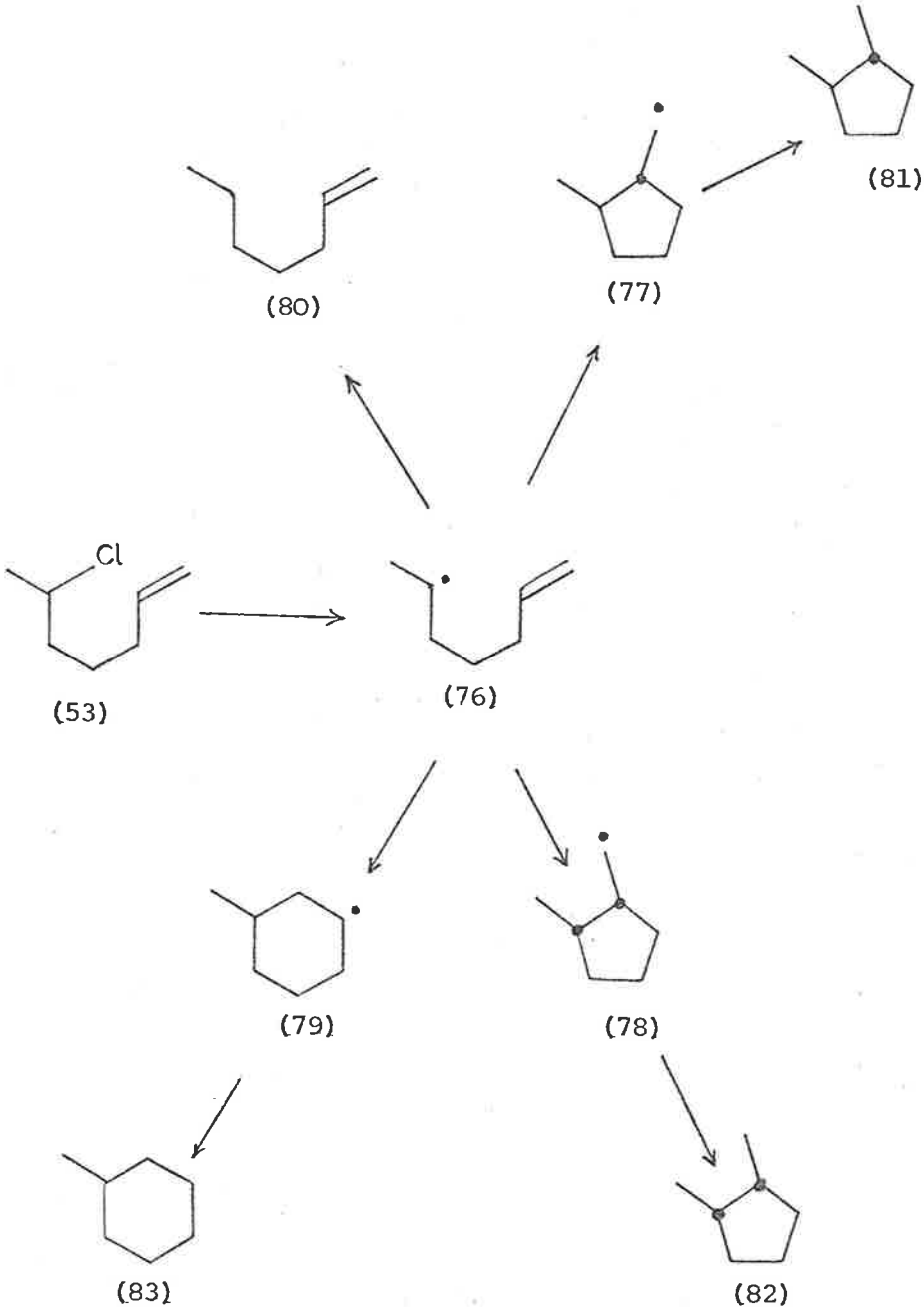
Scheme 36

Table 9

Yield of products from reduction (65°) of 1-(But-3'-enyl)-2-chlorocyclohexane (52) with Tributylstannane in Benzene

$[Bu_3SnH]_o$	.106	.196	.406
but-3-enylcyclohexane (37)	21.4	33.2	49.3
trans-1-methyl-trans-bicyclo[4.3.0]nonane (56)	<0.6	<0.5	<0.3
cis-1-methyl-trans-bicyclo[4.3.0]nonane (57)	3.7	3.4	2.7
trans-1-methyl-cis-bicyclo[4.3.0]nonane (58)	15.9	14.3	10.6
cis-1-methyl-cis-bicyclo[4.3.0]nonane (59)	56.3	47.2	35.9
trans-decalin (74)	1.3	1.0	0.9
cis-decalin (75)	0.7	0.5	0.4
Total yield (%)	77	80	82
(56)/x[a] x 100	.8	.8	.6
(57)/x x 100	4.7	5.1	5.3
(58)/x x 100	20.2	21.4	20.9
(59)/x x 100	71.6	70.7	70.8
(74)/x x 100	1.6	1.5	1.8
(75)/x x 100	0.9	.75	.8

a. x = [(56)+(57)+(58)+(59)+(74)+(75)]



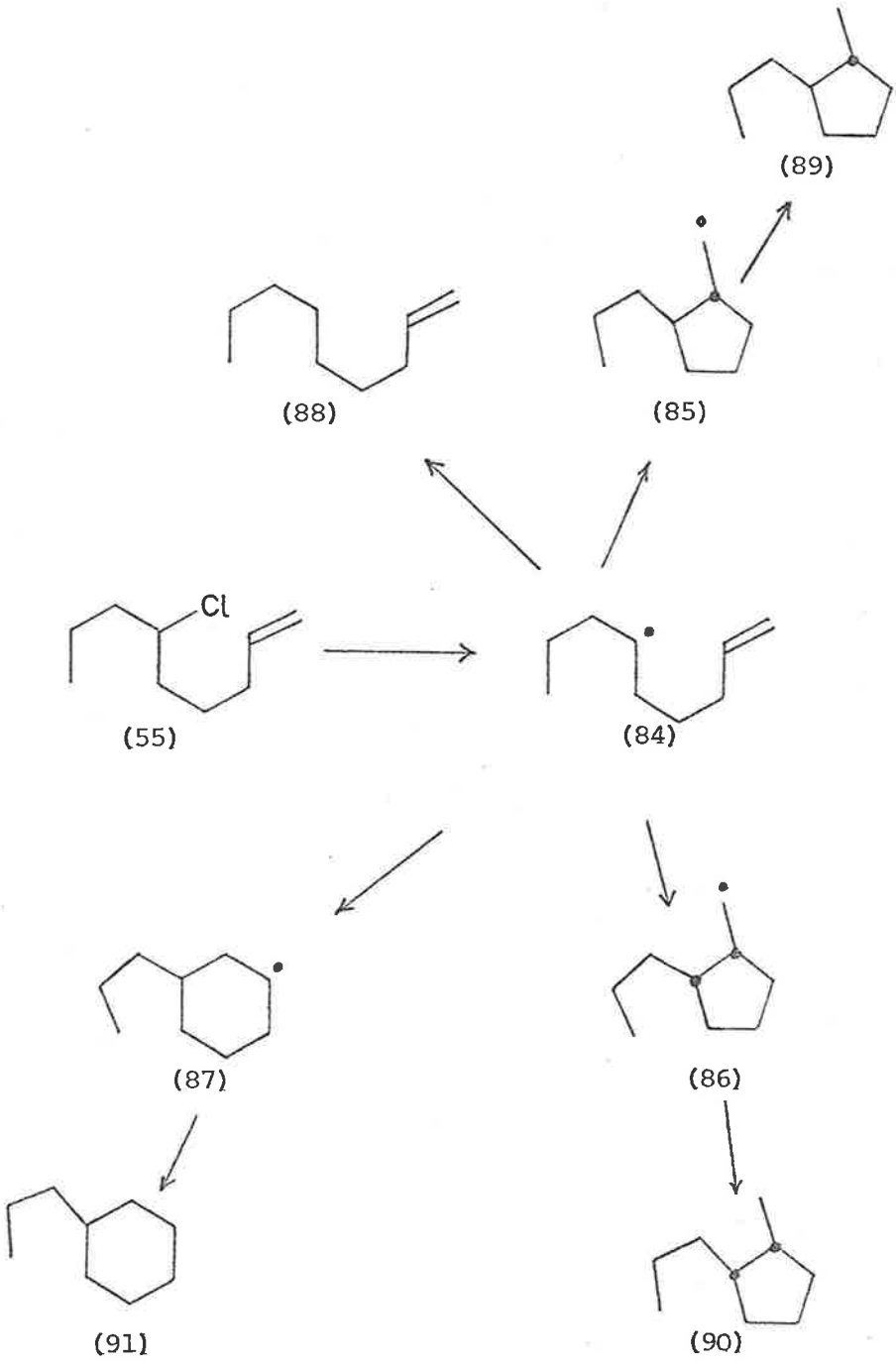
Scheme 37

Table 10

Yield of products from reduction of 6-Chlorohept-1-ene (53) with Tributylstannane in n-Pentane

$[Bu_3SnH]_o$	.074	.15	.43	.43	.48	.43
TEMP (^oC)	65	65	65	35	79.4	103.5
1-heptene (80)	11.9	20.8	41.1	71.9	37.1	31.8
trans-1,2-dimethylcyclopentane (81)	26.8	23.8	19.7	9.6	21.2	24.2
cis-1,2-dimethylcyclopentane (82)	60.7	54.2	38.5	18.5	41.0	43.0
methylcyclohexane (83)	0.8	1.2	0.8	-	0.7	1.1
Total yield (%)	100	100	100	30	100	100
$(81)/x^a \times 100$	30.4	30.1	33.4	34.2	33.7	35.5
$(82)/x \times 100$	68.7	68.4	65.0	65.8	65.2	63.1
$(83)/x \times 100$	0.9	1.5	1.4	-	1.1	1.6

a. $x = [(81)+(82)+(83)]$



Scheme 38

Table 11

Yields of products from reduction (65°) of 6-Chloronon-1-ene (55) with Tributylstannane in Benzene

$[Bu_3SnH]_o$	.094	.193	.374
1-nonene (88)	13.5	23.8	36.1
trans-1-methyl-2-propylcyclopentane (89)	25.8	23.0	19.8
cis-1-methyl-2-propylcyclopentane (90)	60.2	52.8	43.9
propylcyclopentane (91)	0.5	0.4	0.2
Total yield (%)	78	83	84
(89)/x[a] x 100	29.8	30.2	31.0
(90)/x x 100	69.6	69.3	68.7
(91)/x x 100	0.6	0.5	0.3

a. x =[(89)+90)+(91)]

From the Tables 9-11, it can be seen that:

(i) the relative yields of cyclized and uncyclized products are related to the initial concentration of stannane; and

(ii) the cis-trans ratios remain constant within the limit of experimental error.

The data (Table 12) clearly show that for each of the radicals (44), (76) and (84) the cis mode of cyclization is favoured.

Table 12

Stereochemistry for Cyclization of the Radicals (44), (76) and (84)

Radical	cis/trans
(44)	6.9[a], 3.4[b]
(76)	2.3
(84)	2.3

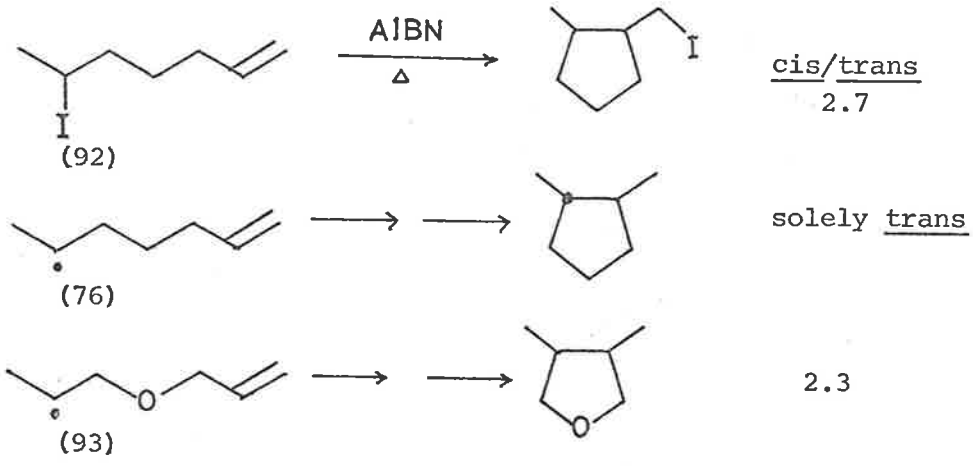
a. trans ring fusion

b. cis ring fusion

The above results are in accord with previous work[64], in which the iodide (92) has been reported to cyclize predominantly to give a cis cyclopentyl derivative. They are however in conflict with a recent report by Walling and Cioffari[50] in which it is suggested that the 6-hepten-2-yl radical (76) undergoes exclusive trans addition*.

* It has subsequently been communicated to us that this report may be in error.

Further work in this department[65] has established that the radical (93) generated from allyl-2-chloropropyl ether cyclizes similarly to the radicals (76) and (84) (Scheme 39).



Scheme 39

It thus appears that cis cyclization may be a general feature of radicals containing the 6-hepten-2-yl system*.

The formation of both trans and cis isomeric products from the relevant precursors may occur via the transition state complexes shown in Fig. 3.

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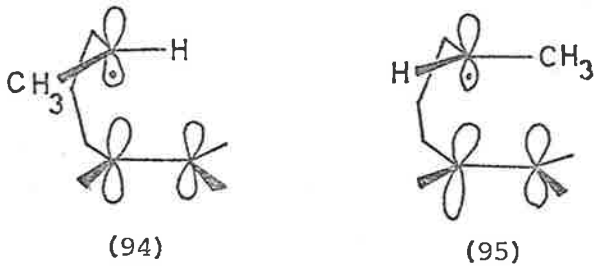
* This statement may not be valid where the cyclization process is reversible.



(94) (95)

Fig. 3

Simple thermodynamic considerations favour the less crowded trans array (94) in preference to the cis (95), since the former is less subject to non-bonded repulsions. The preference for cis cyclization therefore appears to be anomalous, and suggests that such transition state complexes must be reached early and bear no resemblance to the products. Application of orbital symmetry considerations, however, provides an explanation[66].

One model for the transition state for alkyl radical addition to a double bond involves interaction of the half filled p orbital with the vacant π^* orbital[67]. Hyperconjugative mixing[68,69] of the p orbital with adjacent CH σ and σ^* orbitals produces a modified delocalized orbital[69] which is of similar symmetry to the acceptor π^* orbital. A general interaction diagram for the approach of a radical centre to an ethylene is represented in Fig. 4.

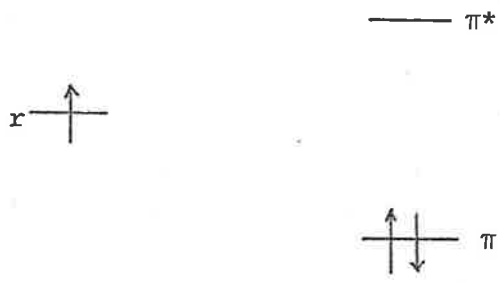


Fig. 4

Secondary effects of the hyperconjugating methyl or methylene group would be two-fold:

(i) to stabilize the r level (which mixes into itself both π and π*);

(ii) to destabilize the π level (which mixes into itself r).

The π level has two electrons in it, the r level one. The above argument is based on the assumption that energy changes are dominated by interactions in the highest occupied level.

Therefore, in the transition state (95) leading to cis disubstituted product the primary mixing of the p and π* orbitals is reinforced by a secondary stabilizing interaction between the alkyl substituent and the olefinic bond (Fig. 5).

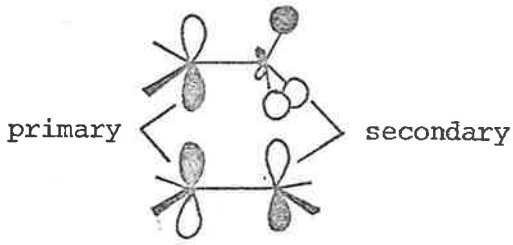


Fig. 5

Only the primary interaction is available to the transition state (94) for trans cyclization and therefore this pathway is energetically less favoured.

Hoffman, Levin and Moss[69] have concluded that the preceding arguments are only valid for highly exothermic association reactions where the transition state occurs at large separation of reaction partners. From a consideration of available bond dissociation energies the reactions described here appear to meet these criteria.

Finally, it is noteworthy that, for all the radicals (44), (76) and (84), the 1,5-direction of ring closure is overwhelmingly preferred. Earlier reports[33,34] suggested that the radical (44) and related species such as (16) tend to undergo 1,6-cyclization leading to trans decalin derivatives. On the basis of the data presented here, these previous findings and the relevant conclusions drawn from them appear to be in error.

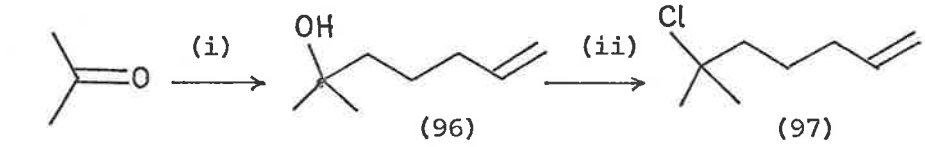
CHAPTER 5

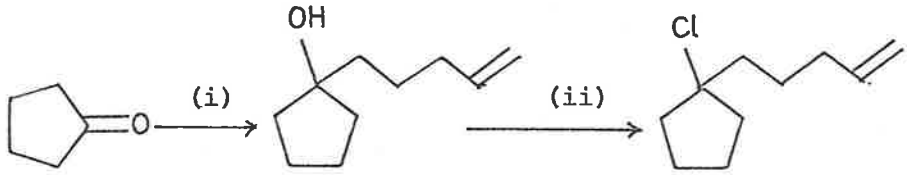
C-1 AND C-6 DISUBSTITUTED 5-HEXENYL RADICALS

CHAPTER 5

C-1 AND C-6 DISUBSTITUTED 5-HEXENYL RADICALS

6-Methyl-6-chlorohept-1-ene (97) and 1-(pent-4'-enyl)-1-chlorocyclopentane (99) were prepared as shown in Scheme 40.

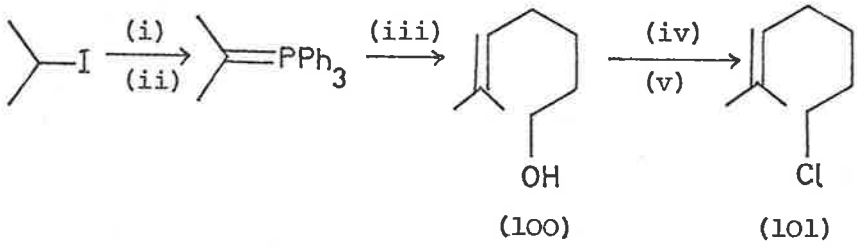




(i) $CH_2=CH(CH_2)_3MgBr/Et_2O$ (ii) $PCl_5/CHCl_3$

Scheme 40

The sequence of reactions shown in Scheme 41 was used to prepare 2-methyl-7-chlorohept-2-ene (101). The present synthesis constitutes a shorter and more efficient route to the alcohol (100), than that previously reported[70].



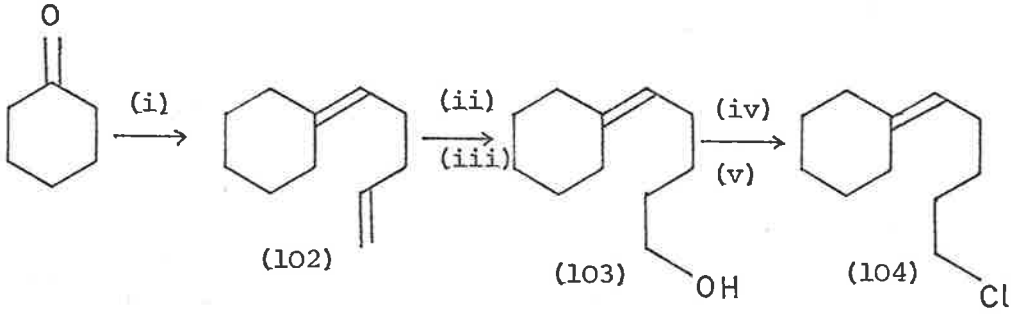
(100) (101)

(i) $PPh_3/120^{o}$ (ii) n-BuLi/Et_2O (iii) $HO(CH_2)_4CHO$

(iv) pTsCl/py (v) py.HCl/DMF

Scheme 41

~~While~~ 1-Cyclohexylidene-5-chloropentane (104) was prepared by the route shown in Scheme 42, using selective hydroboration of the 1,5-diolefin (102) with disiamylborane to form the primary alcohol (103).



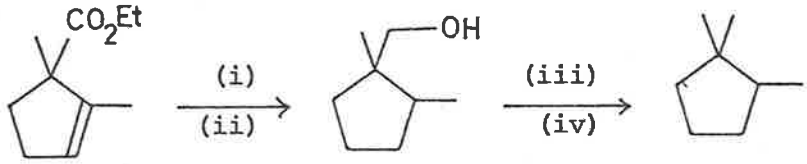
(102) (103) (104)

(i) $CH_2=CH(CH_2)_2CH=PPh_3/Et_2O$ (ii) R_2BH (iii) $H_2O_2/\overline{OH}$

(iv) pTsCl/py (v) py.HCl/DMF

Scheme 42

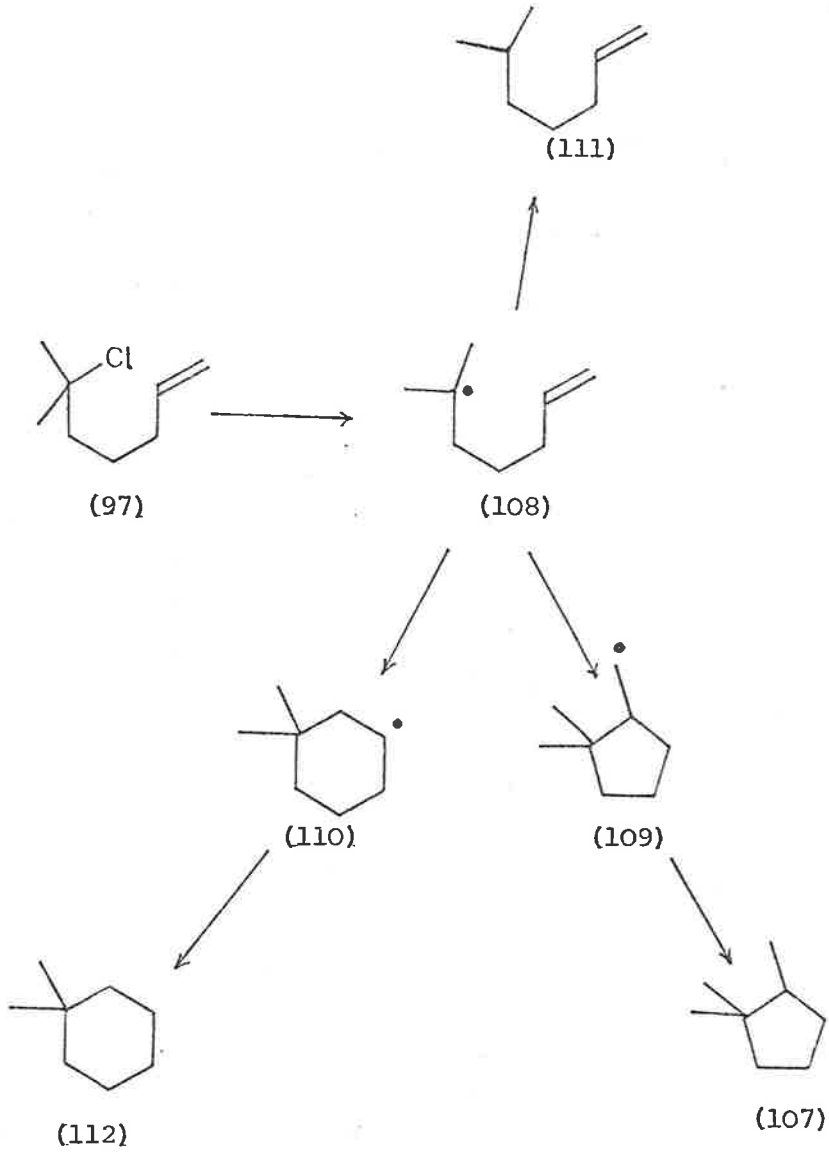
1,1,2-Trimethylcyclopentane (107) was prepared as outlined in Scheme 43. The displacement of the p-toluenesulphonate ester of the alcohol (106) proceeded smoothly, giving very few byproducts.



(105) (106) (107)

(i) $LiAlH_4/Et_2O$ (ii) H_2/PtO_2 (iii) pTsCl/py (iv) $LiAlH_4/Et_2O$

Scheme 43



Scheme 44

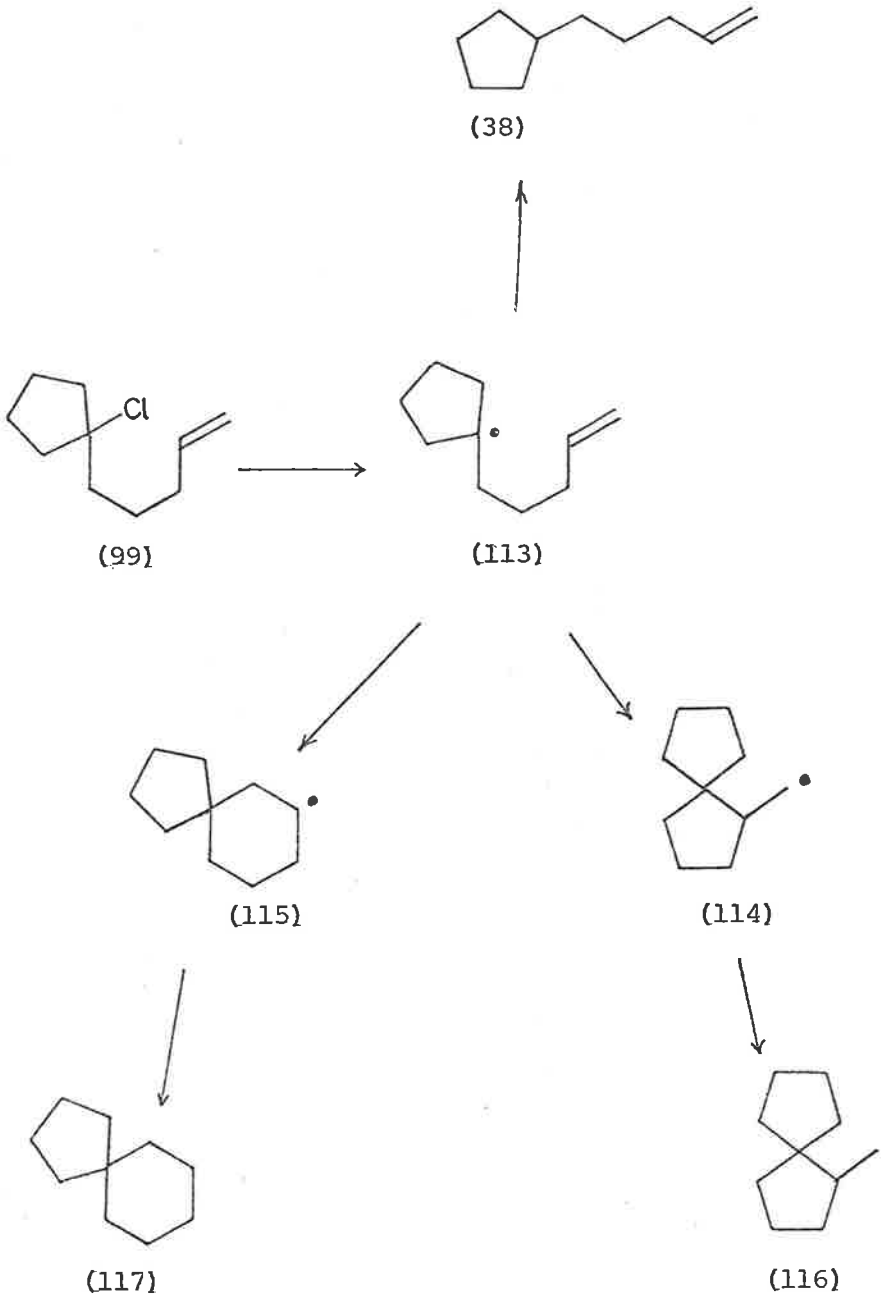
Table 13

Yields of products from reduction (65°) of 6-Methyl-6-chloro-hept-1-ene (97) with Tributylstannane in n-Pentane

$[Bu_3SnH]_o$	.139	.293	.41	.608
6-Methylhept-1-ene (111)	12.2	28.7	34.9	47.5
1,1,2-trimethylcyclopentane (107)	86.3	70.0	64.1	51.3
1,1-dimethylcyclohexane (112)	1.5	1.3	1.0	0.7
Total yield (%)[a]	100	100	100	100
(107)/x[b] x 100	98.3	98.2	98.5	98.7
(112)/x x 100	1.7	1.8	1.5	1.3

a. based on chloride

b. $x = [(107) + (112)]$



(38)

(99)

(113)

(115)

(114)

(117)

(116)

Scheme 45

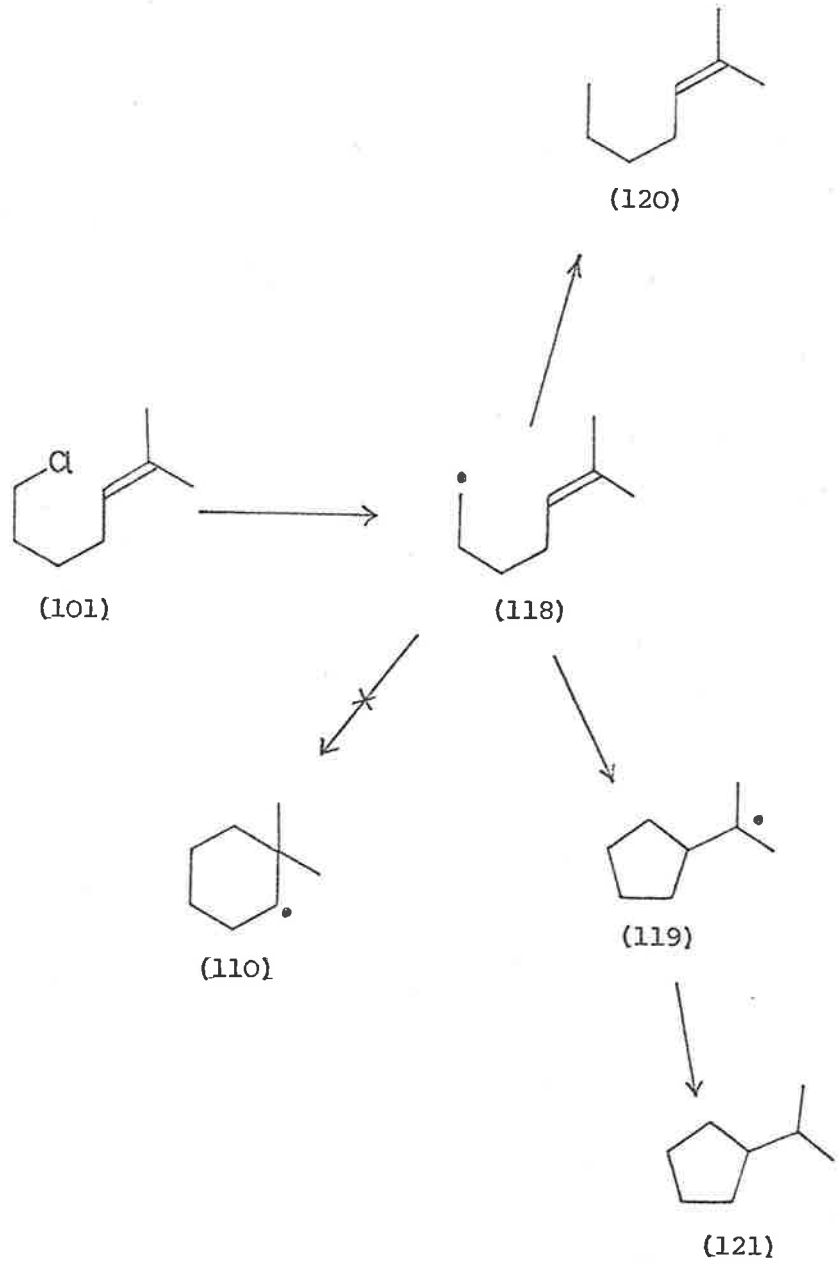
Table 14

Yields of products from reduction (65°) of 1-(Pent-4'-enyl)-1-chlorocyclopentane (99) with Tributystannane in Benzene

$[Bu_3SnH]_o$	.079	.156	.322
Pent-4-enylcyclopentane (38)	13.3	25.2	39.7
1-Methylspiro [4,4] nonane (116)	82.0	70.1	55.4
Spiro [5,4] decane (117)	4.7	4.7	4.9
Total yield (%)[a]	100	100	100
(116)/x[b] x 100	94.6	93.7	91.9
(117)/x x 100	5.4	6.3	8.1

a. based on chloride

b. $x = [(116) + (117)]$



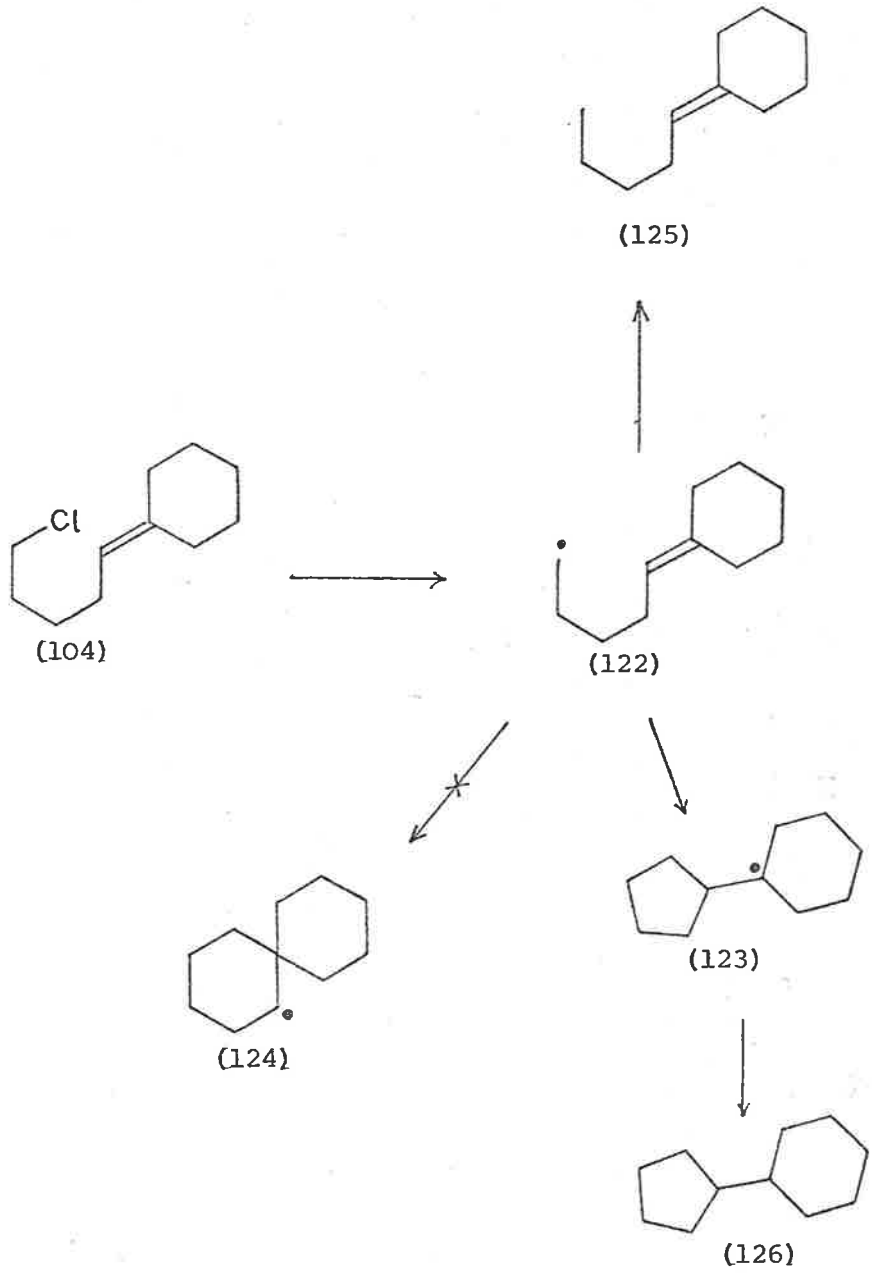
Scheme 46

Table 15

Yield of products from reduction (65°) of 2-Methyl-7-chloro-hept-2-ene (101) with Tributystannane in n-Pentane

$[Bu_3SnH]_o$	.082	.153	.311
2-Methyl-hept-2-ene (120)	3.63	11.97	23.82
isopropylcyclopentane (121)	96.27	88.03	76.18
Total yield (%)[a]	89	80	96

a. based on chloride



Scheme 47

Table 16

Yield of products from reduction (65°) of 1-Cyclohexylidene-5-chloropentane (104) with Tributystannane in Benzene

$[Bu_3SnH]_o$	.113	.193	.427
1-Cyclohexylidenepentane (125)	15.8	24.4	40.9
cyclopentylcyclohexane (126)	84.2	75.6	59.1
Total yield (%)[a]	83	86	87

a. based on chloride

The data summarized in Tables 13-16 indicate that substituents at the radical centre (C-1) and at the double bond terminus (C-6) have little effect on the preferential 1,5-mode of cyclization of 5-hexenyl and related radicals. In fact, as previously noted (Tables 6 and 7), the substituents at C-6 preclude the formation of any detectable amount of 6-membered ring products.

Surprisingly, the cation corresponding to (118) is reported to undergo predominantly 1,5-cyclization.[70] This is a rare example where the radical and carbonium ion precursors lead to similar modes of cyclization, obviously due to the marked stabilization of the tertiary centre in the cyclized product. Another example in the formation of norbornane derivatives[43] (Scheme 19). However, here the positions on the double bond are equivalent and it is not possible to discuss 1,5 or 1,6- ring closure.

It is noteworthy that the yield (ca. 8% of 6-membered ring product (117) from the tertiary radical (113) does not alter with changing stannane concentration and must, therefore, be formed either by rearrangement of the chloride (99) prior to stannane reduction or from an impurity, in the starting

material*. The cyclization of the radical (108) has previously been reported[50] to yield a greater amount (ca. 15%) of 6-membered ring product than found in the present work. Since, in the report[50], its behaviour parallels that for (117), it is considered that its formation occurs by polar mechanisms and not via the cyclized radical (110).

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* The chloride (99) however gave satisfactory microanalytical data and had spectroscopic properties consistent with the proposed structure. Neither of the chlorides (97) and (99) could be analyzed by g.l.c., since they decomposed to yield products which had similar retention times to those of the hydrocarbons (111) and (38) under investigation. These decomposition peaks, however, were resolved from these particular products of the cyclization, and their absence was noted in each study. It is, therefore, concluded that no chloride (97) or (99) remained unreacted at the termination of each reaction.

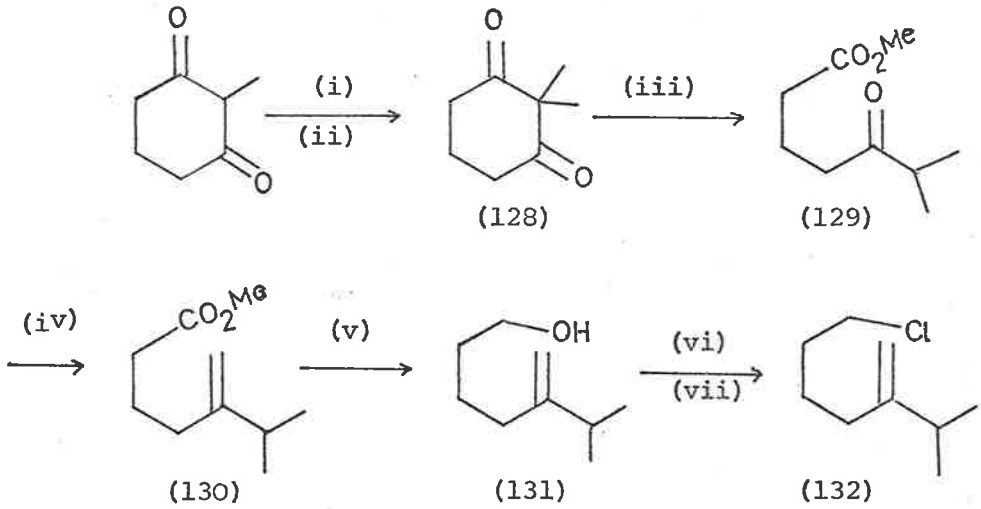
CHAPTER 6

THE 5-ISOPROPYLHEX-5-ENYL AND 5-METHYLHEPT-5-ENYL RADICALS

CHAPTER 6

THE 5-ISOPROPYLHEX-5-ENYL AND 5-METHYLHEPT-5-ENYL RADICALS

2-Isopropyl-6-chlorohex-1-ene (132) was synthesized as shown in Scheme 48.



(i) KOMe/MeOH (ii) MeI (iii) NaOMe/MeOH (iv) $CH_2=PPh_3/Et_2O$

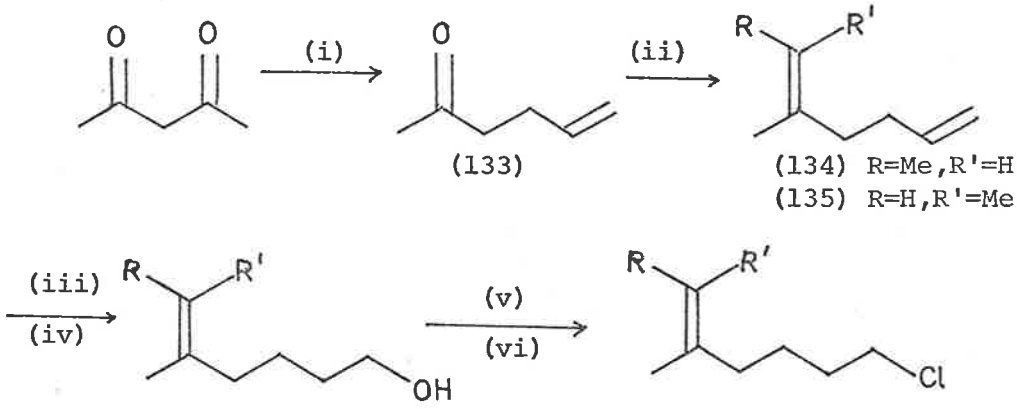
(v) $LiAlH_4/Et_2O$ (vi) pTsCl/py (vii) py.HCl/DMF

Scheme 48

The key step in the sequence was the cleavage of the 1,3-cyclohexanedione (128) to form the keto-ester (129). The apparently straightforward conversion of the keto-ester (129) to the olefinic ester (130), however, proved a difficult task. Although the ylid was generated by a variety of bases, the equilibrium between the reactants and betaine always favoured the former and consequently

the yield of product was low.

An isomeric mixture of trans and cis-3-methyl-7-chlorohept-2-ene (138) and (139) was prepared by the route shown in Scheme 49.

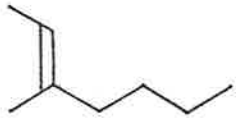


(i) $K_2CO_3/CH_2=CHCH_2Br/EtOH$ (ii) $MeCH=PPh_3/Et_2O$

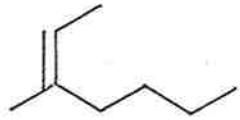
(iii) R_2BH/THF (iv) $H_2O_2/\bar{O}H$ (v) pTsCl/py (vi) py.HCl/DMF

Scheme 49

The assignment of configuration for the geometric isomers is based on the g.l.c. characteristics. It has been established that, for trisubstituted double bonds, the usual order is reversed and the cis isomer has the shorter retention time[71]. In harmony with reported work[72], it was found in the present work that for trans and cis-3-methylhept-2-ene (140) and (141), the cis isomer (141) had a shorter retention time on an Apiezon L capillary column.

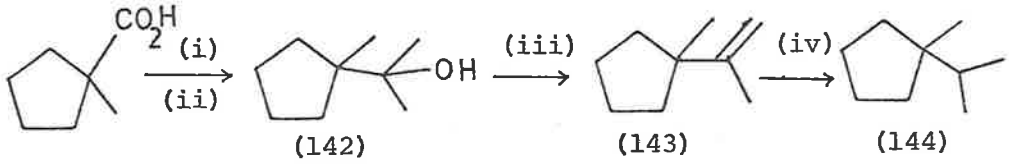


(140)



(141)

1-Isopropyl-1-methylcyclopentane (144) was prepared as shown in Scheme 50.

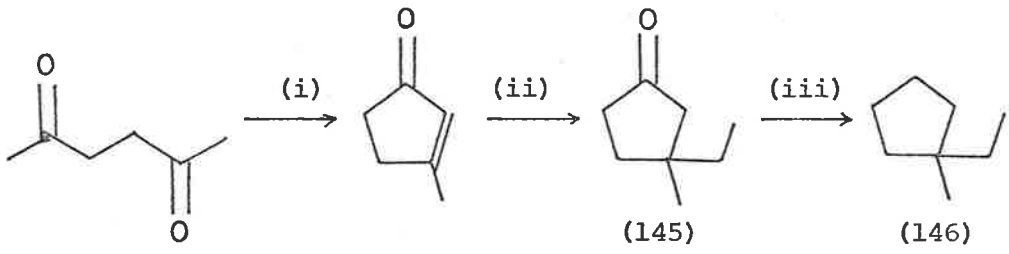


(i) $BF_3.Et_2O/MeOH$ (ii) $MeMgI/Et_2O$ (iii) pTsOH/180° (iv) $H_2/PtO_2/Et_2O$

Scheme 50

Since the use of mild conditions was ineffective, the use of drastic conditions for the elimination of water from the alcohol (142) was required. The product (143), however, was obtained in high yield, relative to a number of byproducts which probably arose from the Meerwein rearrangement of the alcohol (142) under the reaction conditions.

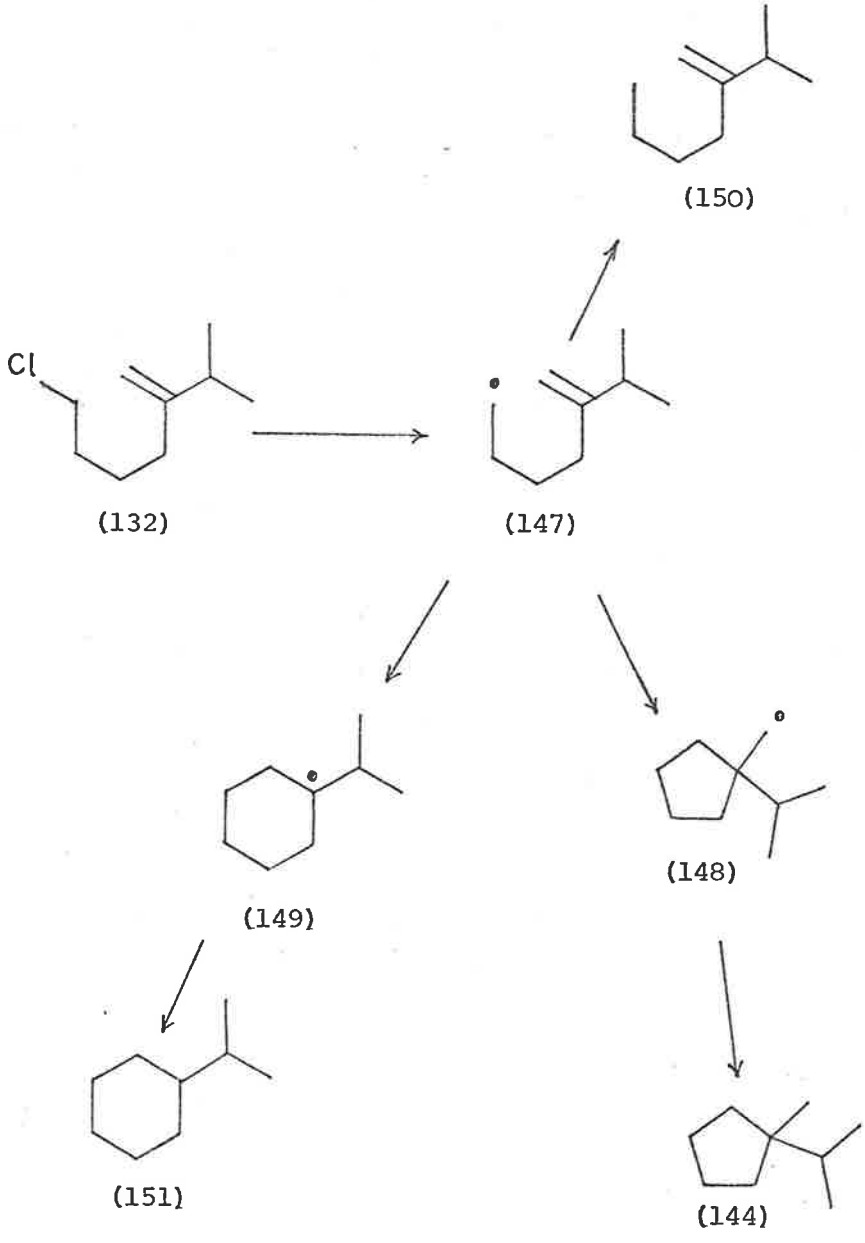
1-Ethyl-1-methylcyclopentane (146) was synthesized as shown in Scheme 51.



(i) $NaOH/H_2O$ (ii) $EtMgI/Cu_2Cl_2/Et_2O$ (iii) Zn/Hg/conc HCl

Scheme 51

In the present work the Clemmensen reduction, although employing strong aqueous acid, has been found superior to the Wolf-Kishner reduction of saturated ketones. The advantages of the Clemmensen reduction are the lower reaction temperatures required and also the easier recovery of the products from the reaction medium. In no cases were there observed any rearrangement products.



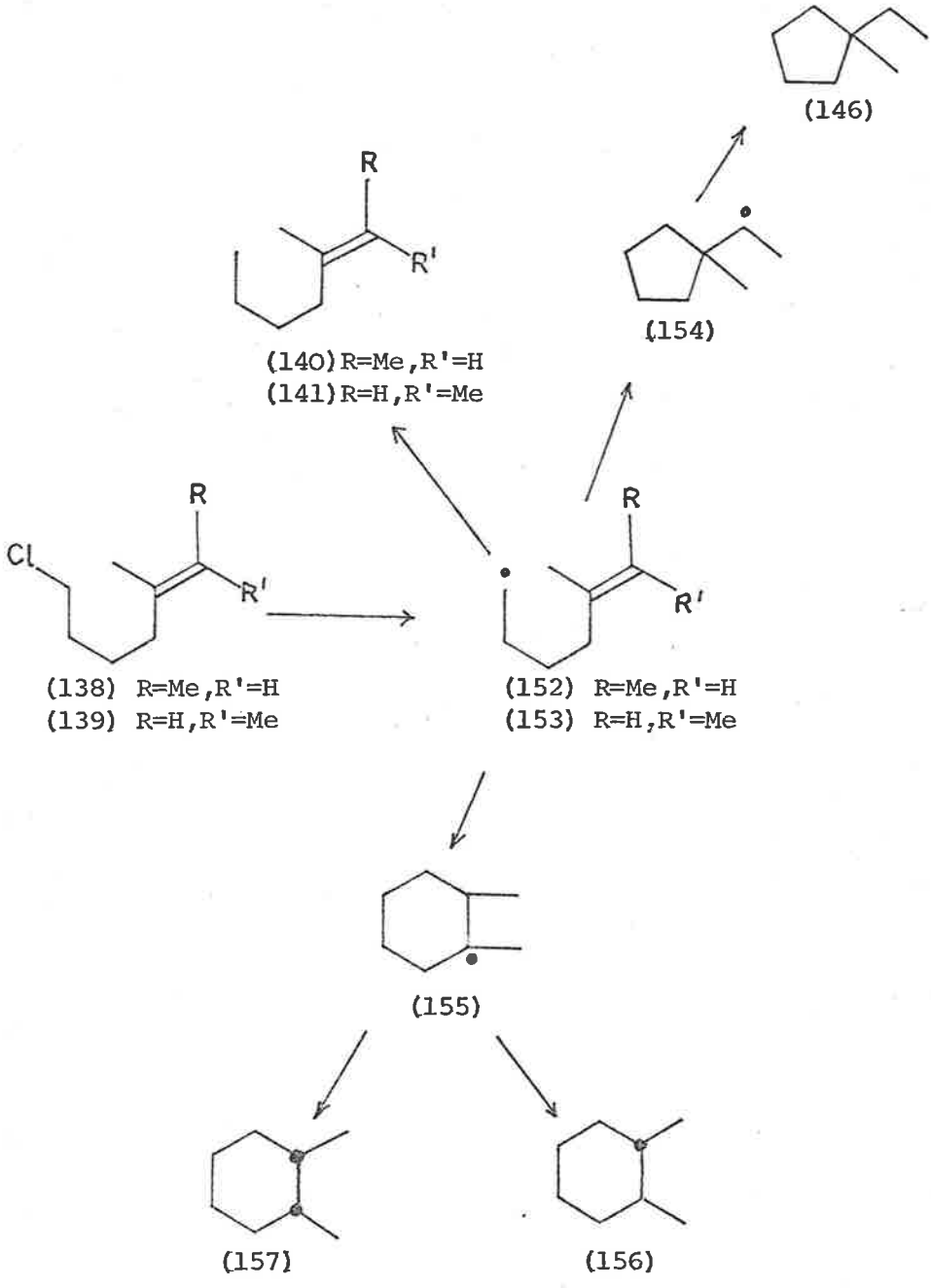
Scheme 52

Table 17

Yield of products from reduction of 2-Isopropyl-7-chloro-hex-1-ene (132) with Tributylstannane in Benzene

Temp (^{o}C)	65	65	65	80.5	97.2
$[Bu_3SnH]_o$	.023	.039	.059	.0494	.0494
2-Isopropyhex-1-ene (150)	30.7	43.9	53.9	42.2	36.0
1-Isopropyl-1-methylcyclo-pentane (144)	16.3	13.2	11.4	13.8	16.1
Isopropylcyclohexane (151)	53.1	43.0	34.7	44.0	60.0
Total yield (%)	73	86	84	70	60
(144)/x[a] x 100	23.5	23.5	24.7	23.9	25.2
(151)/x x 100	76.5	76.5	75.3	76.1	74.8

a. $x = [(144) + (151)]$


(146)
R
R'
(140) R=Me, R'=H
(141) R=H, R'=Me
(154)
Cl
R
R'
(138) R=Me, R'=H
(139) R=H, R'=Me
R
R'
(152) R=Me, R'=H
(153) R=H, R'=Me
(155)
(157)
(156)

Scheme 53

Table 18

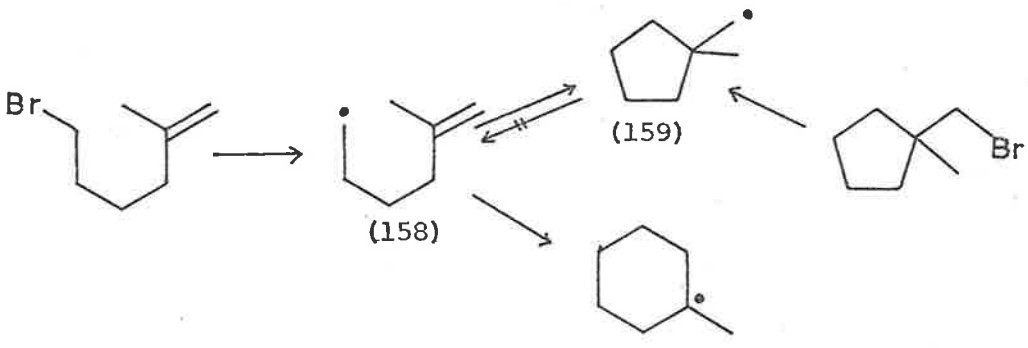
Yield of products from the reduction (65°) of trans and cis-3-methyl-7-chlorohept-2-ene (138) and (139) with Tributylstannane in n-Pentane

$[Bu_3SnH]_o$	.0415	.049	.074	.088
trans-3-methylhept-2-ene (140	13.6	16.0	20.3	23.7
cis-3-methylhept-2-ene (141)	22.6	25.4	30.8	33.3
1-ethyl-1-methylcyclopentane (146)	53.2	50.6	40.9	36.2
trans-1,2-dimethylcyclohexane (156)	6.7	5.0	5.2	4.3
cis-1,2-dimethylcyclohexane (157)	3.9	3.1	2.8	2.5
Total yield (%)	61	70	71	77
$(146)/x^a \times 100$	83.4	86.2	83.6	84.2
$(156) + (157)/x \times 100$	16.6	13.8	16.4	15.8
(156)/(157)	1.7	1.6	1.7	1.8

a. $x = \left[(146) + (156) + (157)\right]$

In contrast to the preceding results, the cyclization of the radicals (147), (152) and (153) is much slower since lower concentrations of stannane must be used to obtain comparable yields of cyclized products. Thus, substitution at C-5 has a very profound effect on the cyclization rate.

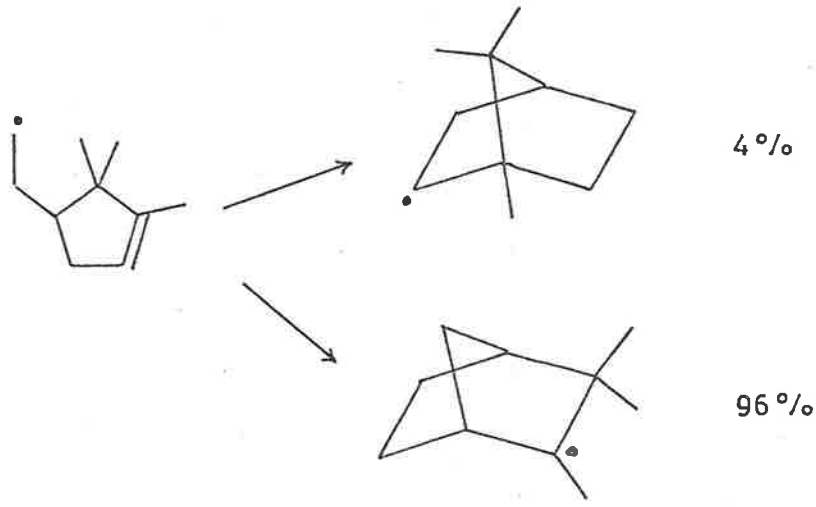
The radical (147) is now seen to cyclize preferentially in the 1,6- direction. This mode of behaviour has been noted before in this department when the radical (158) was shown to undergo 1,6-cyclization[48] (Scheme 54).



Scheme 54

Since the formation of the radical (159) was shown to be irreversible, the above example constitutes one of the first genuine examples of preferential 6-membered ring formation. Previous reports in which 6-membered ring products were formed were a result of thermodynamic control through reversible cyclization processes[33].

An even more dramatic effect of a methyl group on the course of cyclization has been shown recently[73] (Scheme 55).



Scheme 55

In the above example attack at either of the two positions would involve 1,5-cyclization. However, cyclization occurs overwhelmingly away from the methyl-group.

When compared with the effect of the methyl group, the isopropyl group in (147) is seen to increase the relative yield of 6-membered ring products.

The addition of a further methyl group, as in the radicals (152) and (153) is seen to counter the effect of the substituent at C-5 and once again 5-membered ring products dominate. At this stage, it is difficult to decide whether such subtle manifestations

of the product distributions are the result of electronic or steric factors.

Earlier, Julia[33] has reported that the radicals (152) and (153) lead predominantly (> 90%) to 6-membered ring products.

On the basis of his results, he rationalizes the cyclization of species, such as (11) and (13) (Scheme 12), as conforming to the behaviour of the radicals (152) and (153).

Clearly this is not the case, for it has been shown in the present work that 5-membered ring products are preferred from this type of radical species.

The behaviour of compounds, such as (11) and (13) must now be attributed to the presence of the added copper salts, or some unique structural feature of the substrate concerned.

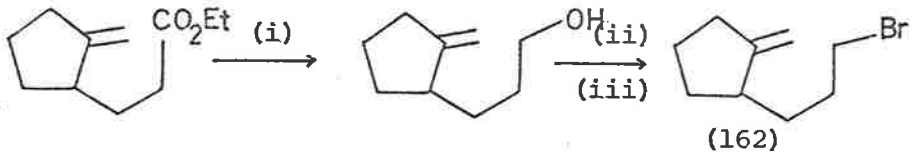
CHAPTER 7

SOME RADICALS LEADING TO BICYCLIC SPECIES

CHAPTER 7

SOME RADICALS LEADING TO BICYCLIC SPECIES

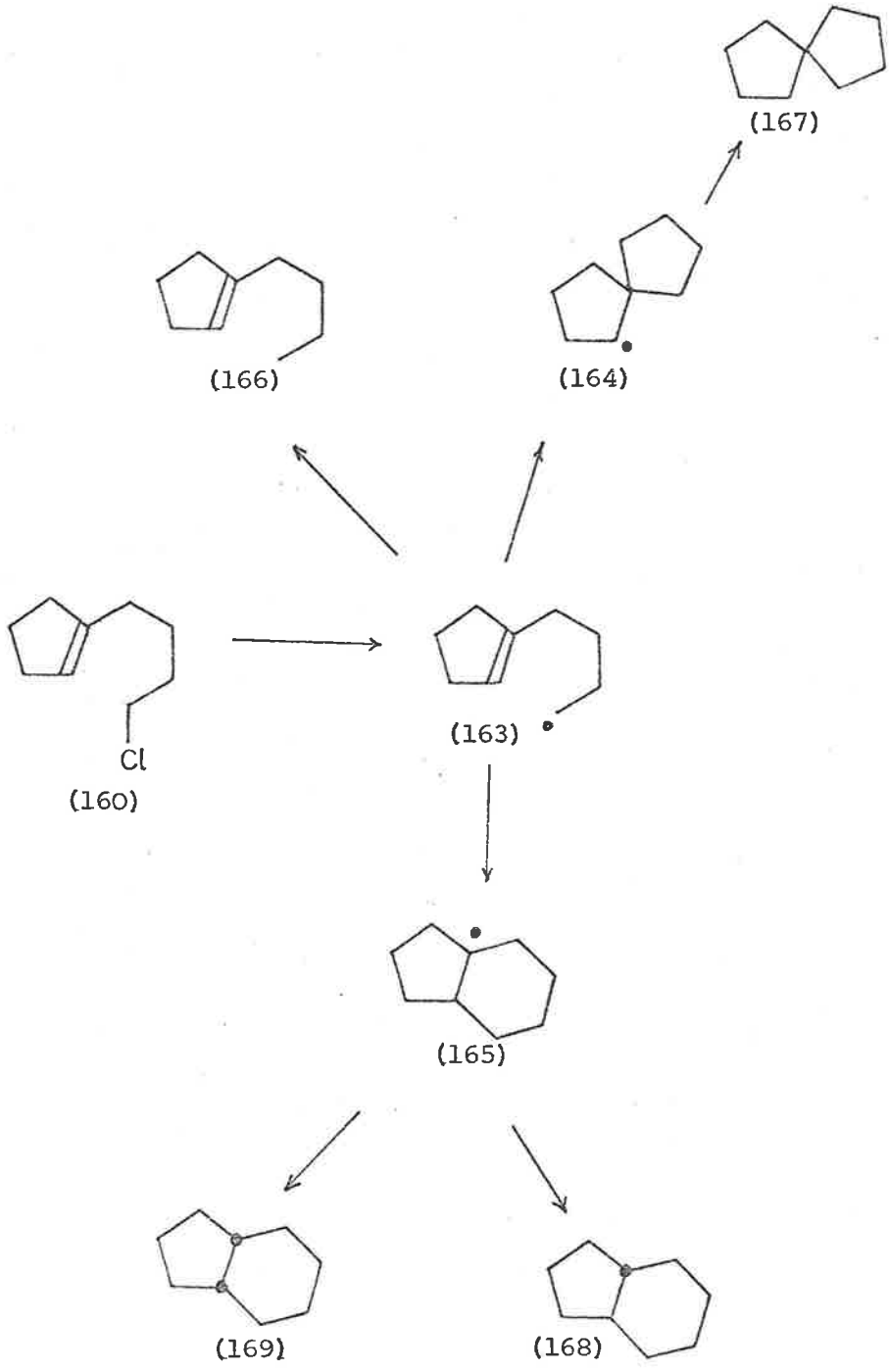
1-(4′-Chlorobut-1′-enyl)cyclopentene (160) and 2-(3′-bromoprop-1′-yl)methylenecyclohexane (161) were available, whilst 2-(3′-bromoprop-1′-yl)methylenecyclopentane (162) was prepared as shown in Scheme 56.



(162)

(i) $LiAlH_4/Et_2O$ (ii) pNsCl/py (iii) py.HBr/DMF

Scheme 56



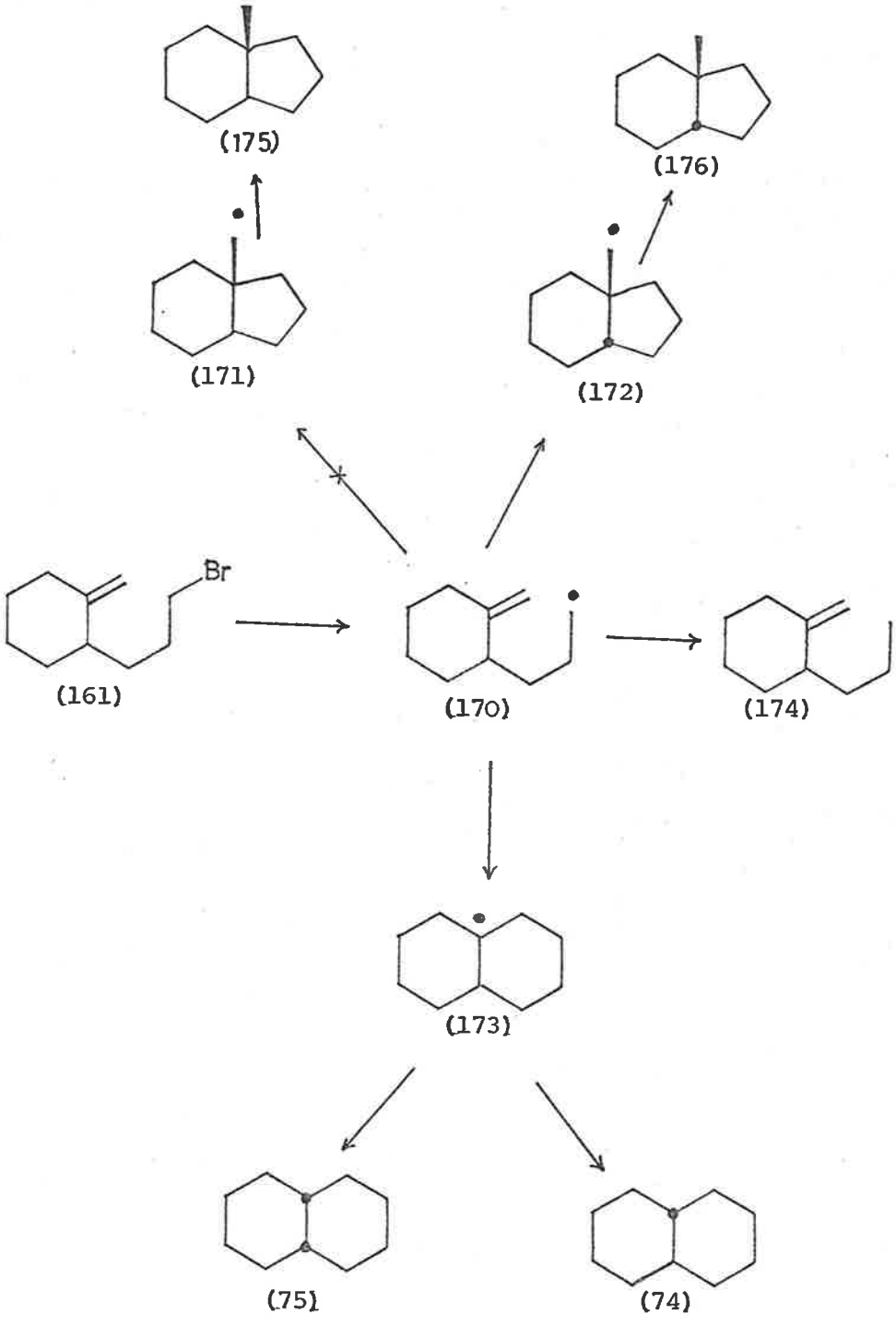
Scheme 57

Table 19

Yields of products from reduction (65°) of 1-(4'-Chlorobut-1'-yl)cyclopentene (160) with Tributylstannane in Benzene

$[Bu_3SnH]_o$	.025	.05	.082
Butylcyclopentene (166)	23.7	39.6	51
Spiro [4,4] nonane (167)	62.8	49.7	40.3
trans-bicyclo [4.3.0] nonane (168)	4.6	3.4	2.8
cis-bicyclo [4.3.0] nonane (169)	8.8	7.2	5.9
Total yield (%)	61	69	75
(167)/x[a] x 100	82	81	82
(168) + (169)/x x 100	18	19	18
(168)/(169)	.52	.47	.47

a. $(x) = \left[(167(+ (168) + (169)\right]$



Scheme 58

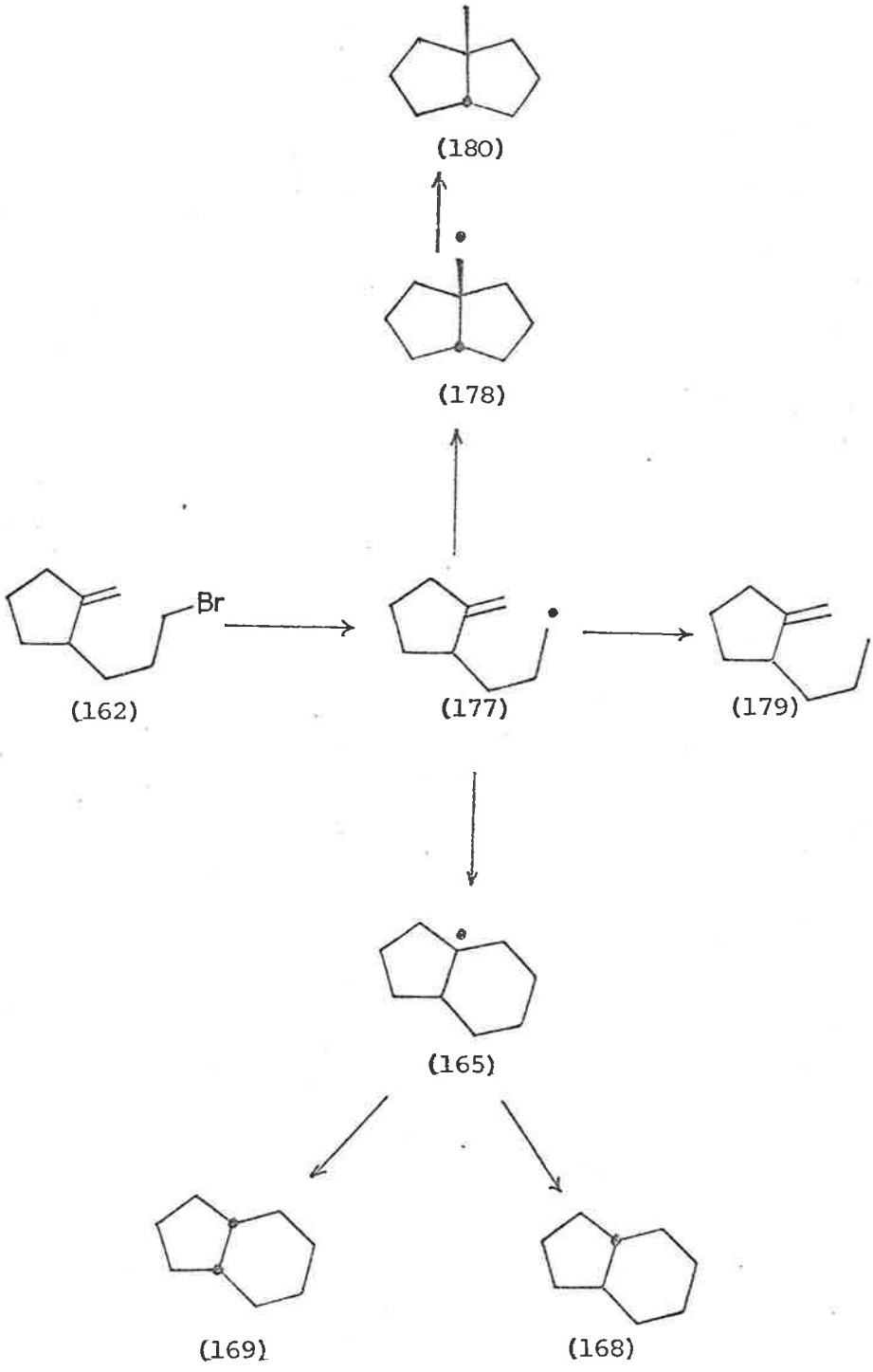
Table 20

Yields of products from reduction (65°) of 2-(3'-Bromopropyl) methylenecyclohexane (161) with Tributylstannane in Benzene

$[Bu_3SnH]_o$	.0179	.051	.082
2-propylmethylenecyclohexane (174)	23.2	45.5	56.0
cis-3a-methylbicyclo [4.3.0] nonane (176)[b]	25.9	18.4	15.1
trans-decalin (74)	43.7	31.1	24.9
cis-decalin (75)	7.3	4.9	3.9
Total yield (%)	68	69	71
(176)/x[a] x 100	33.7	33.8	34.3
(74)+(75)/x x 100	66.3	66.2	65.7
(74)/(75)	6.0	6.3	6.4

a. $x = \left[(176) + (74) + (75)\right]$

b. Although an authentic sample of the isomer (175) was not prepared, its absence was clearly established by g.l.c., based on its reported[62] b.p. and relative retention times.



Scheme 59

Table 21

Yield of products from reduction (65°) of 2-(3'-Bromopropyl) methylenecyclopentane (162) with Tributylstannane in Benzene

$[Bu_3SnH]_o$	.021	.042	.084
2-Propylmethylenecyclopentane (179)	13.2	27.8	47.5
cis-3a-methylbicyclo [3.3.0] octane (180)[a,b]	13.8	16.5	12.5
trans-bicyclo [4.3.0] nonane (168)	21.9	16.6	13.0
cis-bicyclo [4.3.0] nonane (169)	46.1	39.2	27.0
Total yield (%)	65	75	85
(180)/x[c] x100	23	24	25
(168) + (169)/x x 100	77	76	75
(168)/(169)	.48	.42	.48

a. Although an authentic sample was not prepared, the identity of this compound (180) was established by correlation of the relative retention times with three authentic samples of similar hydrocarbons which were kindly donated by the workers who first reported the preparation of (180)[74].

b. The trans isomer is not known.

c. $x = \left[(180) + (168) + (169)\right]$

The mode of cyclization for the radicals (163), (170) and (177), in which the double bond is held by the constraints of a cyclic ring, is seen to be in accord with their corresponding acyclic counterparts. Thus, when the double bond is substituted at C_5, 6-membered ring products predominate, whilst disubstitution enhances 5-membered ring formation.

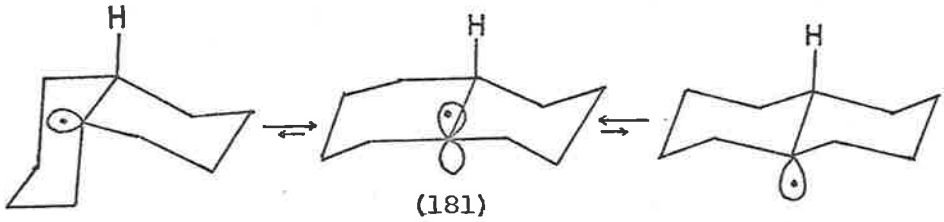
Points of stereochemical interest also become evident. The radicals (170) and (177) cyclize in the 1,5- direction to give bicyclic products containing exclusively a cis fused ring junction. In these examples, the stereochemistry is established at the moment of cyclization, and no equilibration is possible.

Examination of models for the transition state of cyclization reveals that formation of a trans-ring junction is difficult for (170) and impossible for (177), when the limitations of the p-π^* orbital-overlap theory[67] are applied.

A correlation between the p-π^* overlap and the amount of 1,5-cyclization is evident in proceeding from radical (170) to (177).

The constancy of the isomer ratio obtained from the bridge-head radicals (165) and (173) and also the previous tertiary radical (155), over a wide change in stannane concentration indicates that hydrogen-atom transfer to these radicals is a much slower process than the possible conformational changes.

The results obtained from the decalyl radical (173) are in general accord with those previously reported[67,75,76], and are explicable by considering the various conformers available to the radical (Fig. 6).

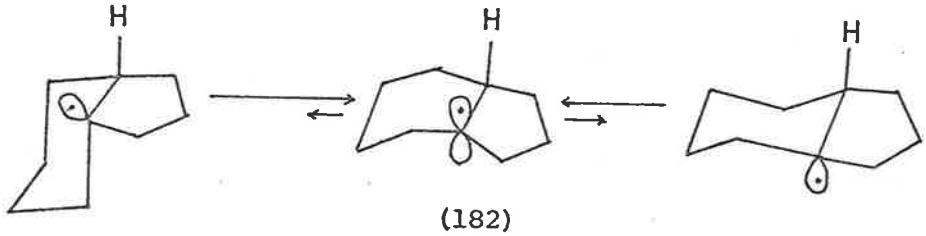


(181)

Fig. 6

The planar decalyl radical (181), due to steric requirements, gives predominantly trans decalin (74).

Although the bicyclo [4.3.0] non-3a-yl radical (165) has not been considered previously, its behaviour is expected to be analogous to the decalyl radical (173). The most stable conformer is expected to be that in which a planar radical centre occurs (182). From an examination of Dreiding models such a conformation (182) appears to be more easily approached from the "top" face, to yield ultimately a cis-fused ring junction (Fig. 7).

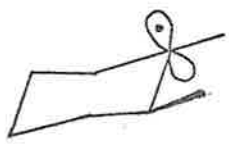


(182)

Fig. 7

These hydrogen-atom transfers to the conformers (181) and (182) are obviously under kinetic control, since for the products from the latter the trans isomer (168) is the more stable.

Finally, it is difficult to rationalize the preferential formation of trans products from the 1,2-dimethylcyclohexyl radical (155). The most stable conformer is expected to be (183), to which hydrogen-atom transfer should occur anti to the methyl group (Fig. 8).



(183)

Fig. 8

The conformer (183) is, however, more flexible than the preceding systems and steric requirements may not be as important in determining the ultimate product distribution.

CHAPTER 8

RATE STUDIES AND ACTIVATION PARAMETERS

CHAPTER 8

RATE STUDIES AND ACTIVATION PARAMETERS

8-1 RATE STUDIES

The values for the overall rate constant for intramolecular cyclization (kc) relative to that for hydrogen-atom transfer from stannane (k_H) were calculated by substituting the results shown in Chapters 3-7 into the integrated rate equation (1) (Table 22). Also included in the Table are the individual rate constants for 1,5- and 1,6-cyclization of the parent radical. The latter were calculated on the assumption that previously determined[46] values of k_H for hexyl, cyclohexyl and t-butyl radicals provide reasonable indices of relative reactivity for the primary, secondary and tertiary radicals used in this study.

Table 22

Rate constants for cyclization of substituted 5-Hexenyl radicals at 65°

Radical	k_c/k_H	$k_{1,5} \times 10^{-6}\ sec^{-1}$	$k_{1,6} \times 10^{-6}\ sec^{-1}$
trans-Deca-5,9-dienyl (43)	.38(.04)[a]	.38	-
cis-Deca-5,9-dienyl (47)	.30(.04)	.30	-
2-(But-3'-enyl)cyclohexyl (44)	.17(.01)	.20	.005
6-Hepten-2-yl (76)	.26(.005)	.31	.005
8-Nonen-4-yl (84)	.29(.01)	.34	.005
2-Methyl-6-Hepten-2-yl (108)	.42(.08)	.31	.005
1-(Pent-4'-enyl)cyclopentyl (113)	.30(.01)	.20[d]	.01[d]
6-Methyl-5-Heptenyl (118)	.70(.3)	.7	-
5-Cyclohexylidenepentyl (122)	.20(.01)	.20	-
5-Isopropyl-5-Hexenyl(147)	.021(.001)	.005	.016
trans and cis-5-Methyl-5-Heptenyl (152),(153)	.028(.003)	.024	.004
4-(Cyclopent-1'-enyl)Butyl (163)	.031(.002)	.025	.006
3-(2'-Methylenecyclohexyl)-propyl (170)	.028(.003)	.009	.019
3-(2'-Methylenecyclopentyl)-propyl (177)	.051(.01)	.012	.039

(Table continued on next page).

Table 22 (continued)

Radical	k_c/k_H	$k_{1,5} \times 10^{-6}\ sec^{-1}$	$k_{1,6} \times 10^{-6}\ sec^{-1}$
5-Hexenyl (1)[b]	.22	.22	.005
5-Methyl-5-Hexenyl (158)[b,c]	.014	.005	.009

a. standard deviation from mean value

b. see ref. 48

c. see ref. 65

d. this value may be in error, see page 69

In obtaining the results in the above Table the total yields of products were normalized to 100% for computational purposes.

Variation in $k_{1,5}$ for the radicals (44), (76), (84), (108) and (113) which differ only in the substitution pattern at C-1 are small and show that substituents at the radical centre have surprisingly little effect on its reactivity. This contrasts with the relatively large differences in the ease of formation between primary, secondary and tertiary radicals reported for weakly exothermic atom-transfer reactions[77], and suggests that in these addition reactions there is little change towards sp^3 hybridization at the transition state.

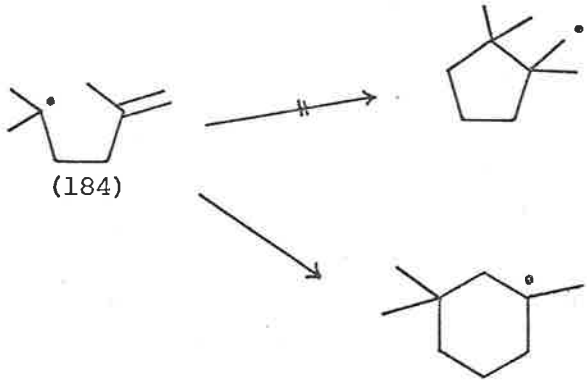
Likewise, substituents at C-6 have also small effects on the rate constant for 1,5-cyclization in the radicals (43), (47), (118) and (122). Since no change occurs in the hybridization of C-6 during the reaction, it is obvious that there is either little disruption of the π bond at the transition state or that the alkyl substituents exert marginal effects on the stability of the developing radical centre at C-6. Examination of models shows that the lower value of $k_{1,5}$ for the cis radical (47), when compared to its isomer (43) is attributed to the greater non-bonded interactions in the transition state of cyclization for the former radical. The low value of $k_{1,5}$ for the radical (122) in comparison to (118) is possibly rationalized as being due to severe steric interactions in the developing product.

The present data do not allow the effects of substituents at C-6 on the rate of 1,6-cyclization to be accurately assessed. It is quite apparent, however, that they retard the reaction strongly.

The presence of substituents on the double bond at C-5 has a profound effect on the rate of 1,5-cyclization; this is reflected in the exceptionally low values of $k_{1,5}$. The predominant formation of 6-membered ring products from these radicals is mainly a consequence of the low $k_{1,5}$ values; the values of $k_{1,6}$ have only marginally increased.

Substitution at C-5 and C-6, as in the radicals (152), (153) and (163) enhances 5-membered ring formation. The values of $k_{1,5}$ have increased marginally while those for $k_{1,6}$ have decreased to the value usually encountered for most systems, for which 5-membered rings are preferentially formed. The effect of the extra methyl group at C-6 is both electronic and steric, the former enhancing 5-membered ring formation, the latter retarding 6-membered ring formation. As a result of the examination of models, it may be concluded that the major retardation observed for radicals substituted at C-5 is in B strain engendered at the 5-carbon by its change towards sp^3 hybridization.

The behaviour of the radical (184) supports this contention[65] (Scheme 60).



(184)

Scheme 60

8-2 ACTIVATION PARAMETERS

Solution of equation (2) by a least squares calculation gave activation parameters for the cyclization processes

$$kc/k_H = e^{-\frac{\Delta\Delta H^{\ddagger}}{RT}} \cdot e^{\frac{\Delta\Delta S^{\ddagger}}{R}} \qquad (2)$$

where $\Delta\Delta H^{\ddagger}$ is enthalpy of activation of cyclization relative to hydrogen-atom transfer from stannane,

and $\Delta\Delta S^{\ddagger}$ is entropy of activation for cyclization relative to hydrogen-atom transfer from stannane.

Table 23

Activation parameters for radical cyclization reactions

acyclic radical	cyclic radical	$\Delta\Delta H^{\ddagger}$ [a]	$\Delta\Delta S^{\ddagger}$ [b]
5-Hexenyl (1)[c]	cyclopentylmethyl (2)	3.0	5.7
	cyclohexyl (3)	4.6	2.9
trans-Deca-5,9-dienyl (43)	1-Cyclopentyl-4-pentenyl (45)	3.12(0.5)[d]	7.17(.14)
6-Hepten-2-yl (76)	cis-2-Methylcyclopentyl-methyl (78)	2.5(.09)	3.94(.26)
	trans-2-Methylcyclopentyl-methyl (77)	3.69(.05)	5.95(.14)
	3-Methylcyclohexyl (79)	4.49(.09)	1.76(.26)
5-Isopropyl-5-hexenyl (147)	1-Isopropylcyclopentyl-methyl (148)	5.22(.11)	4.85(.31)
	1-Isopropylcyclohexyl (149)	4.52(.11)	5.13(.31)

a. $\Delta\Delta H^{\ddagger} = \Delta H^{\ddagger}_{cyc} - \Delta H^{\ddagger}_{H}$ kcal mole^{-1}

b. $\Delta\Delta S^{\ddagger} = \Delta S^{\ddagger}_{cyc} - \Delta S^{\ddagger}_{H}$ e.u.

c. see ref. 48

d. standard deviation from the mean value

The results show that the preferential formation of 5-membered rings is not due solely to favourable entropy terms, as had been previously suggested[78].

The 1,6-cyclization of the radicals (1) and (76) has higher enthalpy and lower entropy values, than that for 1,5-cyclization. The steric interactions involved in attaining the stereo electronic requirements for radical addition probably accounts for the observed trend in the enthalpy of activation while it is generally accepted that there is an ~~increasing~~ increasingly unfavourable loss of entropy on ring-closure with increasing ring size.[130]

The increased value of $k_{1,5}$ for the trans radical (43), relative to the 5-hexenyl radical (1) is caused by a more favourable entropy factor. This mitigates against the concept that substituents at C-6 stabilize the developing radical centre; such an effect would be reflected in a larger enthalpy term.

The results obtained from the radical (147) allow the effects of substituents at C-5 to be more closely dissected. In accord with the earlier proposals that steric compression is important in this type of system, the enthalpy term for 1,5-cyclization increases relative to the other values.

The behaviour of the radical (76) is in keeping with the constraints of orbital symmetry imposed on its cyclization[69]. Thus,

the formation of a cis radical (78) is seen to have a lower enthalpy factor because of the more favourable energetic pathway leading to this isomer. The entropy term, however, is less favourable due to the degree of "ordering" necessary in the transition state to meet the requirements of orbital symmetry.

CHAPTER 9

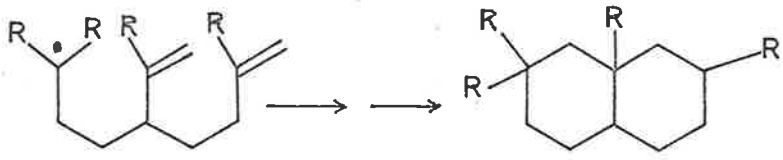
CONCLUSIONS

CHAPTER 9

CONCLUSIONS

Many of the preceding results contrast sharply with earlier reports which suggest that the formation of 6-membered cyclic products is the favoured process. In the area of cyclopolymerization frequent reference is made to their formation[14-16].

In the present work, however, it has been shown that the cyclization of unstabilized 5-hexenyl type radicals, unless substituted at C-5, preferentially affords 5-membered cyclic products. Multiple free-radical cyclizations therefore have limited applicability in the formation of polycyclic structures, unless the substrate is appropriately substituted (Scheme 61).

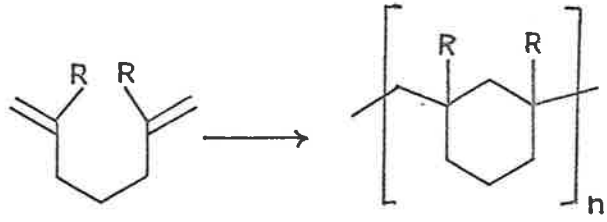


Scheme 61

Studies with the 2-(but-3'-enyl)cyclohexyl radical (44) have established that the stereoselectivity is not very high in the formation of decalin type derivatives. The biosynthetic signifi-

cance of such routes leading to trans-fused polyisoprenoids is therefore very limited.

The cyclopolymerization of dienes, by a free-radical process, will only yield 6-membered rings as the recurring unit when the double bonds of the monomer contain substituents at C-2 and C-6 (Scheme 62).



Scheme 62

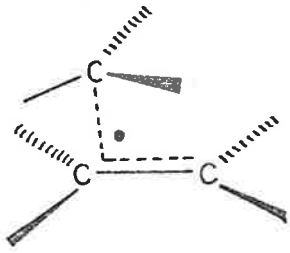
It is noteworthy that, even if the first cyclization in a multi-cyclization pathway is reversible due to the stabilization of the acyclic radical, the subsequent steps must involve unstabilized radicals.

The rates of intramolecular addition reactions in the 5-hexenyl system are seen to be strongly retarded by alkyl substituents at the olefinic centre of attack. These results may have relevance to the mechanism of other reactions involving intermolecular radical addition to olefins. They suggest that the observed

preference for radical addition at the less substituted terminus of an unsymmetrical olefin is due primarily to steric factors and not the stabilizing effect of alkyl substituents on the newly formed radical.

The rate of 1,5-cyclization in the 5-hexenyl radical generally appears to be more sensitive to the effect of substituents at C-5 than those at C-1. This suggests that the transition state is unsymmetrical and involves considerable breaking of the π bond, but little formation of the new σ bond.

The transition state for alkyl addition to an olefinic bond may therefore be seen as comprising a triangular array of centres lying in the same plane as that of the original π bond (185) (Figure 9).



(185)

Fig. 9

This model accords with the previous suggestions[41,42] that the reaction is initiated by interaction of the half-filled p orbital with the vacant π* orbital, a view now supported by the molecular-orbital treatment of the addition of methyl radicals to ethylene[79], and also accommodates the fact that the β scission of cyclopropyl radicals is subject to stereoelectronic control[80]. This final factor becomes obvious when it is considered that fragmentation is the reverse of addition. In any specific system therefore the forward and reverse processes must proceed along the same free-energy profile.

Examinations of models reveal that the preferred arrangement of centres (185) can be more readily attained in the transition states leading to cyclopentylcarbinyl radicals than those leading to cyclohexyl radicals. Therefore systems such as the aryl alkenyl radicals (Table 4) are seen to cyclize preferentially in the 1,5-direction because both conditions for the formation of the transition state may be fulfilled; for 1,6 cyclization only the condition for orbital overlap may be attained. Finally, the demonstration that the preferential cis cyclization of the 6-hepten-2-yl and related radicals is subject to orbital symmetry control provides further strong evidence for the proposed transition state (185).

CHAPTER 10

EXPERIMENTAL

CHAPTER 10

EXPERIMENTAL

10-1 PREAMBLE

General

Melting points were determined using a Kofler hot stage and are uncorrected.

Microanalyses were carried out by the Australian Microanalytical Service, Melbourne.

Organic extracts were dried over magnesium sulphate unless otherwise stated.

Purification by column chromatography was achieved using 1 part of product to 30 parts of ~~support~~ adsorbent.

Light petroleum refers to the fraction of b.p. 30-40°.

Spectroscopic

Infrared spectra were recorded on an Unicam SP200 spectrophotometer and the absorption maxima (cm^{-1}) refer to liquid films. The characteristics of the infrared bonds are expressed as follows: s, strong; m, medium; w, weak; vw, very weak; b, broad.

Nuclear magnetic resonance (n.m.r.) spectra were determined ~~in~~ using carbon tetrachloride solutions, containing tetramethylsilane as an internal standard, with a Varian T60 spectrometer operating at 60 MHz;

data are reported in the order: ~~value~~ chemical shift, integral, multiplicity, coupling constant. The chemical shift is quoted in terms of δ (p.p.m.).

Mass spectra were recorded with an Hitachi Perkin-Elmer RMU-6D spectrometer operating at 70 eV.

Gas liquid chromatography

Routine purity checks were carried out using either a Perkin-Elmer 881 or 990 instrument.

Preparative separations were achieved with either an Aerograph A-705 or a Pye Unicam 104 instrument.

All four instruments were equipped with flame ionization detectors. The following columns were used:

A. F.F.A.P., 3/4%, 6.1m x 3.2mm, steel.

B. Hyprose SP80, 5%, 6.1m x 3.2mm, steel.

C. F.F.A.P., 15%, 3m x 4.2mm, glass.

D. Apiezon L, open tubular, 100m x .503mm, steel.

E. Carbowax 20M-TPA, 15%, 2.4m x 4.2mm, glass.

F. ECWSS-M: Apiezon L (1:1), 15%, 6.1m x 3.2mm, steel.

G. Apiezon M, 5%, 4.6m x 2.1mm, glass.

H. OV-101, 15%, 2m x 6mm, glass.

I. F.F.A.P., 15%, 2m x 6mm, glass.

Tri-n-butylstannane reduction of Halides

The halide, tri-n-butylstannane and an internal standard were accurately weighed into a volumetric flask (5 ml), which was filled with either n-pentane or benzene to give the required concentration. To this solution was added a trace of AIBN. The solution was then pippeted into two ampoules (1 ml) which were cooled to -78°, and sealed under an atmosphere of nitrogen. The ampoules were then heated in an oil-bath at the required temperature for 24 h, at which time they were cooled to -78°, opened and the contents analyzed by g.l.c.

10-2 WORK DESCRIBED IN CHAPTER 3

trans-Deca-5,9-dienol (25)

Disiamylborane[81] [prepared from 2-methylbut-2-ene (4.6g,.066mol) and a 1.9m solution of diborane in tetrahydrofuran (17.6ml, .033mol)] was added dropwise over .5h to an ice-cold solution of trans-deca-1,5,9-triene[82] (24) (4g, .029mol) in tetrahydrofuran (15ml) under an atmosphere of nitrogen. The solution was then stirred for a further 2h at 0°. After the slow addition of water (2ml) the mixture was treated with aqueous sodium hydroxide (3N, 10ml) and then hydrogen peroxide (30%, 10ml) was added at such a rate that the temperature did not exceed 50°. The mixture was then stirred at room temperature overnight, diluted with an excess of water, and then extracted into ether. After the ethereal extract had been washed several times with water, it was dried and concentrated to give a residue which was distilled to yield trans-deca-5,9-dienol (25) (1.5g, 30%), b.p. 48-50°/.005mm (lit[54] 47-49°/.03mm). ν_{max}: 3300 s,b, 1638m, 970s, 910s. G.l.c. analysis (column B, 165°) showed only one component.

Pent-4-enyltriphenylphosphonium Bromide

A mixture of 5-bromopent-1-ene (5g, .034mol) and triphenylphosphine (8.1g, .031mol) in dry nitromethane (30ml) was heated under reflux for 20h. Removal of the solvent left the crude salt which

was purified by being washed several times with dry ether. The salt was thus obtained as a pale-brown solid (11.8g, 90%), m.p. 188-190° (Found: C, 66.64; H, 5.9; Br, 19.4. $C_{23}H_{24}PBr$ requires C, 67.16; H, 5.9; Br, 19.4%).

cis-Deca-5,9-dienol (27)

A suspension of pent-4-enyltriphenylphosphonium bromide (11.5g, .028mol) and potassium t-butoxide (3.1g, .028mol) in dry ether (60ml), under an atmosphere of nitrogen, was stirred at room temperature for 1 h. The resulting deep yellow solution was then treated with a solution of 5-hydroxypentanal (2.75g,.027mol) in ether (10ml) and then stirred for 68h at room temperature. The mixture was then poured into ice-cold water and extracted with ether. The ethereal extract was washed several times with brine ~~solution~~ and then dried. The ether was removed by distillation and the residue was extracted with light petroleum (two filtrations were required to free the extract of solid material). Removal of the light petroleum by distillation through a short column left a liquid which was distilled to give the required alcohol (27) as a colourless liquid (1.46g, 36%), b.p. 50-51°/.01mm (lit.[55] 70° (block)/.03mm). ν_{max} 3350 s,b, 1640m, 920s. G.l.c. analysis (column B, 165°) showed the presence of an impurity (< 5%, R = 0.8) which was identified as the trans alcohol (25) by comparison with an authentic sample.

trans-10-Bromodeca-1,5-diene (28)

trans-Deca-5,9-dienyl p-toluenesulphonate was formed in quantitative yield from the corresponding alcohol (25) by the general procedure given by Fieser[83].

After being kept at room temperature for 24h, a mixture of the p-toluenesulphonate ester (2.15g, .007mol) and pyridinium bromide (2.5g, .016mol) in N,N-dimethyl formamide (25ml) was poured into an excess of ice-cold water and extracted with light petroleum. The light petroleum extract, after being washed thoroughly with water and dried, was concentrated to give a residue which was distilled to yield the bromide (28) (1.0g, 60%) as a colourless liquid b.p. 85° (block)/1.5mm. G.l.c. analysis (column A, 140°) showed the presence of an impurity (ca. 5%), later proven to be the respective chloride (30). Preparative g.l.c. (column I, 150°) gave a pure sample of the required bromide b.p. 90° (block)/2mm. (Found: C, 55.25; H, 8.0. $C_{10}H_{17}Br$ requires C, 55.3; H, 7.9%). ν_{max}: 1640m, 970c, 915s; n.m.r.: 6.00-4.80 (5H, complex), 3.33 (2H, triplet J 6Hz), 2.1-1.33 (10H, complex).

trans-10-Chlorodeca-1,5-diene (30)

Using the above procedure, ~~except~~ excepting that pyridinium chloride was used in the displacement step, the alcohol (25) (.85g) was converted into trans-10-chlorodeca-1,5-diene (30) (.45g, 50%), b.p.

65-70° (bath)/6mm. (Found: C, 69.5; H, 9.8. $C_{10}H_{17}Cl$ requires C, 69.55; H, 9.9%). ν_{max}: 1640 m, 975s, 920s, 655m; n.m.r.: 6.0-4.83 (5H, complex), 3.5 (2H, triplet J 6Hz), 2.27-1.33 (10H, complex and overlapping). G.l.c. analysis (column A, 140°) showed that no impurities were present.

cis - 10-Bromodeca-1,5-diene (29)

Utilizing the procedure for the preparation of the trans bromide (28), cis-deca-5,9-dienol (27) (1.2g) was converted into its respective bromide (29 (1.7g, 98%). G.l.c. analysis (column A, 140°) established the presence of an impurity (ca. 10%) deemed to be the chloride (31). Preparative g.l.c. (column C, 150°) followed by distillation in a "bubble" tube gave cis-10-bromo-deca-1,5-diene as a colourless liquid, b.p. 80-85° (block)/1.5mm. (Found: C, 55.15; H, 7.7. $C_{10}H_{17}Br$ requires C, 55.3; H, 7.9%). ν_{max}: 1640m, 920s; n.m.r.: 6.0-4.8 (5H, complex), 3.33 (2H, triplet J 6Hz), 2.17-1.33 (10H, complex).

cis-Deca-1,5-diene (34)

A suspension of pent-4-enyltriphenylphosphonium bromide (9g, .022mol) and potassium t-butoxide (2.46g, .022mol) in dry ether (50ml) was stirred at room temperature for 1 h. The resulting deep yellow solution was treated with a solution of pentanal (1.9g, .022mol) in ether (10ml) and then stirred for a further 24h at room temperature.

The mixture was poured into ice-cold water and then extracted with ether. The ethereal extract was washed with brine ~~solution~~ and then dried. The ether was removed by distillation and the residue was then chromatographed on Sorbsil. Elution with light petroleum gave cis-deca-1,5-diene (34) (1.8g, 60%) ~~on~~ as a colourless liquid b.p. 50° (bth)/15mm, n_o^{25} 1.4361 (Found: C, 86.5; H, 13.0. $C_{10}H_{18}$ requires C, 86.9; H, 13.1%). ν_{max}: 1635m, 910s; n.m.r.: 6.0-4.83 (5H, complex), 2.1 (6H, triplet J 2Hz), 1.3 (4H, complex), 0.9 (3H, distorted triplet J ca 5Hz), mass spectrum: m/e 138 (trace), 55 (100%). G.l.c. analysis (column D, 140°) showed only one component indicating that the expected trans-deca-1,5-diene (33) impurity was not resolvable under the analytical conditions.

But-3-enylcyclohexane (37)

Cyclohexylcarbinol was prepared by lithium aluminium hydride reduction of cyclohexanecarboxylate and coverted into the bromide (35) b.p. 74-75°/14mm (lit.[84] 93-94°/38mm) by treatment with phosphorus tribromide[57].

A solution of allyl bromide (1.6g, .013mol) and cyclohexylmethyl magnesium bromide [freshly prepared from magnesium (.5g, .02mol) and the bromide (35) (2.5g, .014mol) in tetrahydrofuran (15ml) in tetrahydrofuran (30ml), was treated at 0° with a solution of dilithium tetrachlorocuprate[53] (.4ml) and then stirred for a further

3h. The mixture was then treated with excess ammonium chloride solution and extracted with light petroleum. After the light petroleum extract had been washed with brine ~~solution~~, it was dried and concentrated to give a residue which was distilled to yield but-3-enylcyclohexane (37) (.9g, 60%) as a colourless liquid b.p. 55-60° (bth)/14mm, n_D^{20} 1.4519 (lit.[85] 58.6-60°/15.5mm, n_D^{25} 1.4521). ν_{max}: 1640m, 980m, 900s; n.m.r.: 6.12-5.5 (1H, complex), 5.1-4.83 (2H, complex), 2.33-1.0 (15H, complex, broad and overlapping); mass spectrum: m/e 138 (5%), 55 (100%). G.l.c. analysis (column D, 140°) showed the product to be homogeneous.

Pent-4-enylcyclopentane (38)

Cyclopent-2-enyl acetic acid (10g) was converted to 2-cyclopentylethanol (6g, 66%), b.p. 82-83°/17mm (lit.[86] 79-82°/10mm) by reduction at room temperature with lithium aluminium hydride followed by hydrogenation.

Treatment of the p-toluenesulphonate ester of the alcohol with lithium bromide gave the bromide (36) in 72% yield as a colourless liquid b.p. 68-70°/16mm (lit.[87] 76-78°/19mm).

Using the procedure described for the preparation of the olefin (37), the bromide (36) (6.5g) was converted into pent-4-enylcyclopentane (3.8g, 83%) b.p. 62-63°/14mm, n_D^{20} 1.4478 (Found: C, 86.6; H, 13.1. $C_{10}H_{18}$ requires C, 86.9; H, 13.1%). ν_{max} 1638m, 990m, 910s; n.m.r.: 6.0-5.4 (1H, complex), 5.03-4.8 (2H, complex), 2.0-1.0

(15H, complex), mass spectrum: m/e 138 (4%), 67 (100%). G.l.c. analysis (column D, 140°) showed that no impurities were present.

Cyclopentylcyclopentane (41)

2-Cyclopentylcyclopentanone (4.6g, .03mol), potassium hydroxide (4g, .07mol), hydrazine hydrate (5ml, 90%) and diethylene glycol (30ml) were heated at 170° under reflux for 9h. The mixture was then cooled, diluted with water and extracted with light petroleum. Distillation of the washed and dried extract afforded a residue which was chromatographed on Sorbsil. Elution with light petroleum gave cyclopentylcyclopentane (41) (1.8g, 48%), b.p. 74-75°/15mm, n_D^{20} 1.4642 (lit.[88] 190-190.5/762mm, n_D^{20} 1.4642). Mass spectrum m/e 138 (12%), 68 (100%). G.l.c. analysis (column D, 140°) showed the compound to be pure. Further elution with ether:light petroleum (1:1) gave a solid which was recrystallized from acetone to yield the azine (42) (1g, 25%) as white, needle-like crystals m.p. 76-76.5°. (Found: C, 79.6; H, 10.9; $C_{20}H_{32}N_2$ requires C, 79.9; H, 10.7%). ν_{max}: 1650m; mass spectrum: m/e 300 (trace), 232 (65%), 164 (100%).

10-3 WORK DESCRIBED IN CHAPTER 4

trans-2-(But-3'-enyl)cyclohexanol (50) was prepared in 40% yield by the literature procedure[55]. N.m.r.: 6.0-5.5 (1H, complex), 5.1-4.8 (2H, complex), 3.2 (1H, broad singlet), 2.0-1.0 (14H, complex). G.l.c. analysis (column A, 145°) showed that no impurities were present.

cis and trans-2-(But-3'-enyl)cyclohexanol (50)

Reduction of 2-(but-3'-enyl)cyclohexanone (48)[89] with lithium aluminium hydride gave 2-(but-3'-enyl)cyclohexanol (50) (91%) as a colourless liquid b.p. 98-100°/13mm (lit.[54] 76-77°/2mm). N.m.r.: 6.0-5.5 (1H, complex), 5.1-4.8 (2H, complex), 3.8 (≃ .3H, ~~sharp~~ singlet showing very fine splitting), 3.2 (≃.7H, broad singlet), 2.0-1.0 (14H, complex). G.l.c. analysis (column A, 145°) showed the product to be a mixture of trans and cis isomers (2:1, R = 0.9).

1-(But-3'-enyl)-2-Chlorocyclohexane (52) [Mixture of cis & trans isomers]

To a stirred solution of phosphorus pentachloride (2.4g, .0114mol) in chloroform (5ml) at -78°, was added 2-(but-3'-enyl) cyclohexanol (50) (0.8g, .0052 mol) in chloroform (20ml). The resulting mixture was allowed to equilibrate to 0° during 1h and then ice-water was added. The chloroform layer was separated, washed successively with water, saturated aqueous sodium bicarbonate and then

dried ($CaCl_2$). The solvent was removed by distillation to leave a residue which was chromatographed on Florisil. Elution with light petroleum gave a colourless liquid (.73g, 76%) which was shown by g.l.c. analysis (column A, 140°) to be > 90% pure. Subsequent preparative g.l.c. (column I, 140°) gave pure 1-(but-3'-enyl)-2-chlorocyclohexane (52) as a colourless liquid b.p. 75-78° (block)/4.5mm. (Found: C, 69.3; H, 10.1. $C_{10}H_{17}Cl$ requires C, 69.55; H, 9.9%). ν_{max}: 1640m, 920s; n.m.r.: 6.0-5.5 (1H, complex), 5.2-4.8 (2H, complex), 4.3 (≃ .6H, distorted sharp singlet), 3.5 (≃.4H, broad singlet), 2.1-1.3 (13H, complex).

6-Chlorohept-1-ene (53)

6-Hepten-2-ol (5g) was converted into the chloride (53) (2.2g, 48%) by the literature procedure[61]. G.l.c. analysis (column F, 115°) however, showed a number of impurities. Preparative g.l.c. (column E, 130°) gave pure 6-chloro-hept-1-ene (53) as a colourless liquid b.p. 50-55°/22mm, n_D^{22} 1.4374 (lit.[61] 148-150°, n_D^{20} 1.4385). The spectral characteristics were identical with those reported[61].

8-Nonen-4-ol (54)

A solution of 5-bromopent-1-ene (8.3g, .056 mol) in dry ether (25ml) was added dropwise with stirring to magnesium (1.8g, .055mol) in dry ether (5ml). After formation of the Grignard reagent was complete, butanal (3.7g, .051mol) in ether (10ml) was added drop-

wise at 0°. The reaction mixture was then stirred overnight, cooled to 0°, and saturated ammonium chloride solution (7ml) added such that the temperature did not exceed 15°. The ethereal solution was decanted from the precipitated magnesium salts and then dried. The ether was distilled off to leave a residue which was further distilled to yield 8-nonen-4-ol (54) (4.5g, 63%), b.p. 91-95°/13mm. (Found: C, 76.3; H, 12.8. $C_9H_{12}O$ requires C, 76.0; H, 12.8%). ν_{max}: 3350s, 1640s, 1000s, 920s; n.m.r.: 6.0-5.5 (1H, complex), 5.1-4.8 (2H, complex), 3.5 (1H, broad), 2.0 (2H, broad), 1.3 (9H, complex), 0.93 (3H, distorted triplet 3 5Hz). G.l.c. analysis (column A, 130°) showed the product to be homogeneous.

6-Chlorononon-1-ene (55)

Utilizing the phosphorus pentachloride procedure, described for the preparation of the chloride (52), 8-nonen-4-ol (54) (3.5g) was converted into 6-chlorononon-1-ene (55) (1.5g, 38%), b.p. 74-76°/13mm. (Found: C, 67.1; H, 10.4. $C_9H_{17}Cl$ requires C, 67.3; H, 10.7%). ν_{max}: 1640s, 1000s, 920s; n.m.r.: 6.0-5.3 (1H, complex), 5.1-4.8 (2H, complex), 3.6 (1H, broad), 2.2-1.5 (10H, complex), 0.9 (3H, distorted triplet J 5Hz). G.l.c. analysis (column A, 100°) showed the product to be pure.

1-Methylene-Bicyclo [4.3.0] non-3a(7a)-ene (60)

A suspension of methyltriphenylphosphonium iodide (4.0g,

.01mol) and potassium t-butoxide (1.12g, .01mol) in dry ether (25ml), under an atmosphere of nitrogen was stirred at room temperature for 1h. The resulting deep yellow solution was treated at 0° with a solution of bicyclo [4.3.0] non-3a(7a)-en-1-one[90] (1.3g, .008mol) in ether (5ml) and then stirred a further 5h at room temperature. The reaction mixture was then poured into ice-cold water and extracted with ether. The ether was removed and the residue extracted with light petroleum and washed with 80% aqueous ethanol and then dried. Removal of the solvent by distillation left a residue which was distilled to yield 1-methylene-bicyclo [4.3.0] non-3a(7a)-ene (60) (.41g, 40%) as a colourless liquid b.p. 60° (bath)/15mm. ν_{max}: 1640s, 1620s, 850s,830m; n.m.r.: 4.5 (2H, singlet), 2.4-1.5 (12H, complex); mass spectrum: m/e 134 (57%), 91 (100%). A satisfactory analysis could not be obtained.

1-Methylene-Bicyclo [4.3.0] nonane (62)

Utilizing the previous procedure except that the crude product was chromatographed on Sorbsil and eluted with light petroleum, cis-bicyclo [4.3.0] nonan-1-one (61) (1.67g) was converted into 1-methylene-bicyclo [4.3.0] nonane (62) (1.35g, 83%), b.p. 60° (bath)/ 14mm. (Found: C, 87.9; H, 11.6. $C_{10}H_{16}$ requires C, 88.2; H, 11.8%). ν_{max}: 1650s, 890s; n.m.r.: 4.7 (2H, broad and complex), 2.4-1.2 (14H, complex); mass spectrum: m/e 136 (50%), 95 (100%), 79 (80%). G.l.c.

analysis (column F, 120°) showed the product to be a mixture of isomers (ca. 2:1, R = .91).

1-Hydroxymethylene-trans-bicyclo [4.3.0] nonan-2-one (65)

Utilizing the general literature procedure[91], trans-bicyclo [4.3.0] nonan-2-one (64)[92] (3.5g) was converted into 1-hydroxymethylene-trans-bicyclo [4.3.0] nonan-2-one (65) (3.8g, 90%). The crude product was allowed to react with excess cupric acetate in aqueous methanol to give the copper chelate in 80% yield. A sample recrystallised from acetone had m.p. 232-234 (dec.). ν_{max}: 1610s, 1490s; mass spectrum: m/e 166 (49%), 138 (100%), 137 (38%).

The hydroxymethylene ketone (65) could be recovered in 95% yield by shaking the chelate with a mixture of dilute sulphuric acid (10%, aqueous) and ether. The product so obtained was a pale yellow liquid which darkened rapidly on exposure to air.

1-Thiobutylmethylene-trans-bicyclo [4.3.0] nonan-2-one (66)

A solution of 1-hydroxymethylene-trans-bicyclo [4.3.0] nonan-2-one (65) (1.4g, .008mol), n-butanethiol (.86g, .01mol) and p-toluenesulphonic acid (ca .01mg) in benzene (25ml) was refluxed under a nitrogen atmosphere with continuous separation of water for 3.5h. The resulting solution was concentrated and the residual oil

extracted with ether. The ethereal extract was washed with saturated aqueous sodium bicarbonate, brine and then dried. Removal of the solvent gave a dark red liquid which was distilled to give 1-thiobutyl-methylene-trans-bicyclo [4.3.0] nonan-2-one (66) (1.3g, 70%) as a pale yellow liquid b.p. 150-155° (block/.1mm. (Found: C, 70.6; H, 9.5. $C_{14}H_{22}OS$ requires C, 70.55; H, 9.3%). ν_{max}: 1700s, 1595s.

1-Methyl-trans-bicyclo [4.3.0] nonan-2-one (67)

A mixture of the thiobutylmethylene ketone (66) (1.3g) and Raney nickel (≃ 30g) in ethanol (100 ml) was heated for 3 h at 70°. The catalyst was removed by filtration and the solvent distilled off to leave a yellow liquid. The crude material was then dissolved in ether and oxidized by the procedure of Brown[93]. Work-up in the usual manner gave a liquid which was distilled to yield 1-methyl-trans-bicyclo [4.3.0] nonan-2-one (67) (.53g, 60%) as a very slightly yellow liquid b.p. 90-95° (block)/13mm. ν_{max} 1730s. G.l.c. analysis (column A, 140°) showed the product to be a mixture of epimers (ca 6:1, R = 1.28).

The semicarbazone was obtained as a white crystalline solid m.p. 185-187°. (Found: C, 63.0; H, 9.0; N, 20.0. $C_{11}H_{19}N_3O$ requires C, 63.1; H, 9.15; N, 20.1%).

The Imine (68)

A mixture of trans-bicyclo [4.3.0] nonan-2-one (64) (1g, .0072mol), cyclohexylamine (.75g, .0074mol) and p-toluenesulphonic

acid (trace) in benzene (20ml) was refluxed under a nitrogen atmosphere with continuous separation of water for 20 hr. The solvent was removed to leave a liquid which was distilled to yield the imine (68) (1.7g, 100%) as a viscous liquid b.p. 100-105° (block)/0.01mm. (Found: C, 81.8; H, 11.3. $C_{15}H_{25}N$ requires C, 82.1; H, 11.5%). ν_{max} 1770s.

Attempted preparation of 1-Methyl-trans-bicyclo [4.3.0] nonan-2-one (6

Attempted conversion of the imine (68) to the desired product (67) utilizing the general procedure developed by Stork[94], resulted only in the recovery of trans-bicyclo [4.3.0] nonan-2-one (64) (88%).

1-Methyl-bicyclo [4.3.0] nonane

Hydrogenation of the diene (60) or the olefin (62) gave 1-methyl-bicyclo [4.3.0] nonane in quantitative yield, as a mixture of isomers (column D, 140°), which had b.p. 60° (bth)/14mm, n_D^{25} 1.4658 (lit.[62] 168-185°, n_D^{20} 1.4690).

trans-1-Methyl-cis-bicyclo [4.3.0] nonane (58) and cis-1-Methyl-cis bicyclo [4.3.0] nonane (59)

A pure sample of each of these compounds was kindly donated by Professor Heimbach.

trans-1-Methyl-trans-bicyclo [4.3.0] nonane (56) and cis-1-Methyl-trans-bicyclo [4.3.0] nonane (57).

A mixture of 1-methyl-trans-bicyclo [4.3.0] nonan-2-one (67) (.25g, .0017mol) and zinc amalgam (1.9g) in concentrated hyd rochloric acid (3ml), was heated under reflux for 1.5h. The reaction mixture was then cooled and extracted with n-pentane. The n-pentane extract was washed successively with conc. sulphuric acid, water, aqueous sodium carbonate and then dried ($CaCl_2$). The solvent was removed by distillation at atmospheric pressure to leave a residue which was chromatographed on Sorbsil. Elution with light petroleum gave a colourless liquid which was further purified by preparative g.l.c. (Column I, 100^{o}) to give a homogeneous sample of trans-1-methyl-trans-bicyclo [4.3.0] nonane (56) n_D^{25} 1.4589. Mass spectrum: m/e, 138 (22%), 96 (52%), 67 (100%). cis-1-Methyl-trans-bicyclo [4.3.0] nonane (57) was the only other component formed, however, its yield relative to the other isomer was so low ($\simeq$ 1%) that it could not be isolated.

trans-Decalin (74) and cis-Decalin (75)

Authentic samples of each of these compounds were available from previous work in this department.

1-Heptene (80), trans-1,2-dimethylcyclopentane (81), cis-1,2-dimethylcyclopentane (82) and methylcyclohexane (83) were all commercially available.

1-Nonene (88)

Utilizing the procedure described for the preparation of 1-methylene-bicyclo [4.3.0] nonane (62), octanal was converted into 1-nonene (88) (55%) b.p. 35-40° (block)/13mm. n_D^{25} 1.4149 (lit.[95] 146.9°, n_D^{25} 1.4133).

trans-1-Methyl-2-propylcyclopentane (89) and cis-1-methyl-2-propyl-cyclopentane (90)

1-Methylene-2-propylcyclopentane (179) was hydrogenated in the presence of Adams' catalyst to give a quantitative yield of the two isomers (89) and (90). The isomers, separated by preparative g.l.c. (column H, 90°) had the following constants:

trans-1-Methyl-2-propylcyclopentane (89) n_D^{20} 1.4275 (lit.[95] 1.4274)

cis-1-Methyl-2-propylcyclopentane (90) n_D^{20} 1.4339 (lit.[95] 1.4343)

n-Propyl cyclohexane (91)

The crude product obtained from the Grignard coupling of bromocyclohexane and allyl bromide was hydrogenated to yield a liquid which was purified by preparative g.l.c. (column E, 110°) to give a pure sample of n-propylcyclohexane (91) n_D^{20} 1.4370 (lit.[95] n_D^{20} 1.43705)

10-4 WORK DESCRIBED IN CHAPTER 5

2-Methyl-6-Hepten-2-ol (96)

5-Bromopent-1-ene (8.3g, .056mol) in dry ether (25ml) was added dropwise (2h) with stirring to magnesium turnings (1.3g, .055mol) in dry ether. After formation of the Grignard reagent was complete acetone (3.1g, .054mol) in dry ether (10ml) was added at 0^{o} during 1h, followed by stirring at room temperature for 15h. The mixture was then cooled to 10^{o} and saturated ammonium chloride solution (ca 20ml) added dropwise such that the temperature did not exceed 15^{o}. The ether layer was then decanted off and the residue extracted with more ether. The combined ethereal extracts were then dried. Removal of the solvent by distillation left a residue which was distilled to yield 2-methyl-6-hepten-2-ol (96) (5.0g, 73%) as a colourless liquid b.p. $76-80^{o}$/23mm (lit.[96] 69^{o}/17mm). ν_{max}: 3380s, 1640m, 920s; n.m.r.: 6.0-5.6 (1H, complex), 5.1-4.9 (2H, complex), 1.4 (4H, complex), 1.1 (6H, singlet). G.l.c. analysis (column A, 100^{o}) showed no impurities.

6-Chloro-6-Methylhept-1-ene (97)

Utilizing the phosphorus pentachloride procedure the alcohol (96) (3.3g) was converted into 6-chloro-6-methylhept-1-ene (97) (1.43g, 38%) b.p. $54-55^{o}$/17mm. (Found: C, 65.9; H, 10.2. Calc. for $C_8H_{15}Cl$: C, 65.5; H, 10.3%). N.m.r.: 6.0-5.5 (1H, complex), 5.1-4.9 (2H, complex), 2.2-1.7 (12H, complex). The chloride (97) decomposed on

attempted g.l.c. analysis.

1-(Pent-4'-enyl)cyclopentanol (98)

Using the procedure described for the conversion of acetone into the alcohol (96), cyclopentanone (10g) was converted into 1-(pent-4'-enyl)cyclopentanone (98) (9.6g, 53%) b.p. 52-58°/.2mm. (Found: C, 77.9; H, 11.6. $C_{10}H_{18}O$ requires C, 77.9; H, 11.8%). ν_{max}: 3350s, 1640s, 1000s, 910s; n.m.r.: 6.0-5.5 (1H, complex), 3.2-4.8 (2H, complex), 2.2-1.9 (15H, complex and broad). G.l.c. analysis (column G, 150°) showed the product to be pure.

1-(Pent-4'-enyl)-1-chlorocyclopentane (99)

Using the procedure developed for the preparation of the chloride (52), the alcohol (98) (4g) was converted into 1-(pent-4'-enyl)-1-chlorocyclopentane (99) (3.3g, 73%), b.p. 68°/2.5mm. (Found: C, 69.2; H, 9.8. $C_{10}H_{17}Cl$ requires C, 69.55; H, 9.9%). ν_{max}: 1640s, 990s, 910s; n.m.r.: 6.0-5.5 (1H, complex), 5.2-4.8 (2H, complex), 2.2-1.5 (14H, complex). The chloride (99) could not be analyzed by g.l.c.

6-Methyl-5-Hepten-1-ol (100)

n-Butyllithium (15ml of a 1.87m solution in n-hexane, .028mol) was added slowly to a stirred suspension of isopropyltriphenyl phosphonium iodide[97] (10g, .023mol) in ether (20ml) and stirring was continued until solution appeared complete (1h). The dark red solu-

tion was cooled to 0° and 5-hydroxypentanal[98] (2.35g, .023mol) in ether (5ml) added over a .5h period. The mixture was then allowed to equilibrate to room temperature and stirred for a further 16h. A work-up procedure as described for the preparation of the alcohol (27) gave 6-methyl-5-hepten-1-ol (100) (.84g, 29%) as a colourless liquid b.p. 100-105° (block)/16mm. (lit.[70] 82-104°/22mm). ν_{max}: 3350s, 1060s; n.m.r.: 5.1 (1H, triplet J 6Hz), 3.5 (2H, triplet J 6Hz), 2.2-1.5 (13H, complex). G.l.c. analysis (column A, 135°) showed no impurities to be present.

2-Methyl-7-Chlorohept-2-ene (101)

6-Methyl-5-Hepten-1-ol (100) (.8g) was converted into 2-methyl-7-chlorohept-2-ene (101) (.48g, 50%) b.p. 75-80° (block)/15mm. (Found: C, 65.8; H, 10.3. $C_8H_{15}Cl$ requires C, 65.5; H, 10.3% by displacement of its p-toluenesulphonate ester with pyridinium chloride. N.m.r.: 5.1 (1H, triplet J 6Hz), 3.6 (2H, triplet J 6Hz), 2.2-1.6 (12H, distorted doublet). G.l.c. analysis (column A, 95°) showed the product to be homogeneous.

5-Cyclohexylidenepent-1-ene (102)

Utilizing the previously described procedure for the conversion of pentanal into cis-deca-1,5-diene (34), cyclohexanone (2.74g) was converted into 5-cyclohexylidenepent-1-ene (102) (2.4g, 60%), b.p. 80° (blk)/14mm. (Found: C, 87.9; H, 12.3. $C_{11}H_{18}$ re-

quires C, 87.9; H, 12.1%). N.m.r.: 6.0-5.5 (1H, complex), 5.2-4.8 (3H, complex), 2.1 (8H, triplet J 4Hz), 1.6 (6H, singlet). G.l.c. analysis (Column G, 135°) showed < 1% impurity.

5-Cyclohexylidenepentan-1-ol (103)

Utilizing the procedure for the preparation of trans-deca-5,9-dienol (25) from trans-deca-1,5,9-triene (24), 5-cyclohexylidenepent-1-ene (102) (2.3g) was converted into 5-cyclohexylidenepentan-1-ol (103) (.65g, 25%), b.p. 78°/.14mm. N.m.r.: 5.0 (1H, triplet J 6Hz), 3.6 (2H, triplet J 6Hz), 2.1-1.1 (17H, complex). G.l.c. analysis (column A, 175°) showed the product to be > 94% pure.

1-Cyclohexylidene-5-Chloropentane (104)

Displacement of the p-toluenesulphonate ester of the alcohol (103) with pyridinium chloride by the usual procedure gave 1-cyclohexylidene-5-chloropentane (75%) as a colourless liquid b.p. 55-60° (bath)/.1mm. (Found: C, 71.0; H, 10.4. $C_{11}H_{19}Cl$ requires C, 70.8; H, 10.3%). N.m.r.: 5.0 (1H, triplet J 6Hz), 3.3 (2H, triplet J 6Hz), 2.0-1.3 (16H, complex). G.l.c. analysis (column A, 150°) showed the product to be > 97% pure.

1,1,2-Trimethylcyclopentane (107)

Ethyl-1,2-dimethylcyclopent-2-ene carboxylate[99] (105) (1.8g) was converted into 1,2-dimethycyclopentylcarbinol (106) (1.2g, 90%), b.p. 80-85° (block)/14mm by reduction at room temperature with lithium aluminium hydride followed by hydrogenation at 40 p.s.i. in the presence of Adams' catalyst. G.l.c. analysis (column A, 130°) showed the product to be a mixture of isomers (3:1, R = .65).

1,2-Dimethylcyclopentylcarbinol (106) (.75g) was converted into p-toluenesulphonate ester in the usual manner[83], and allowed to rea with lithium aluminium hydride (.3g) in ether at reflux temperature for 44h. A working-up procedure as usual[100] gave a brown oil which was distilled to yield 1,1,2-trimethylcyclopentane (107) (.38g, 85%). G.l.c. analysis (column G, 70°) showed the presence of five impurities (10%). Preparative g.l.c. (column H, 75°) gave a pure sample of the hydrocarbon (107) n_D^{25} 1.4208 (lit.[95] n_D^{25} 1.42051) N.m.r.: 1.5 (7H, broad and complex), .97 (3H, singlet), .91 (3H, doublet J 5Hz), .75 (3H, singlet); mass spectrum: m/e, 112 (22%), 69 (78%), 56 (100%).

6-Methylhept-1-ene (111)

3-Methylbutan-1-ol (6g) was converted into 3-methylbutyl bromide (7.5g, 75%), b.p. 117-119° (lit.[101] 121.3-121.6) by treatment

of
~~by~~ its p-toluenesulphonate ester with lithium bromide in N,N-dimethyl formamide.

Using the procedure described for the preparation of but-3-enylcyclohexane (37), 3-methylbutylbromide (3.1g) was converted into 6-methylhept-1-ene (111) (2.9g, 100%). A pure sample isolated by preparative g.l.c. (column H, 65°) had n_D^{20} 1.4072 (lit.[95] n_D^{20} 1.4070). N.m.r.: 6.0-5.5 (1H, complex), 5.1-4.8 (2H, complex), 2.1-1.2 (7H, broad and complex), 0.87 (6H, doublet J 6Hz).

1,1-Dimethylcyclohexane (112) was prepared according to the literature procedure[102]. G.l.c. analysis (column G, 70°) showed the compound to be homogeneous.

1-Methylspiro [4,4] nonane (116)

Using the procedure described for the preparation of the olefin (62), spiro [4,4] nonan-1-one (1g) was converted into 1-methylenespiro [4,4] nonane, b.p. 55-60° (block)/16mm. (Found: C, 88.3; H, 11.8. $C_{10}H_{16}$ requires C, 88.2; H, 11.8%). N.m.r.: 4.7 (2H, distorted triplet, J < .5Hz), 2.3 (2H, broad), 1.7 (12H, singlet showing fine splitting); mass spectrum. m/e 136 (22%), 95 (87%), 79 (100%). G.l.c. analysis (column G, 120°) showed no impurities.

A mixture of 1-methylenespiro [4,4] nonane (.3g) and Adams' catalyst (.020g) in ether (10ml) was shaken in the presence

of hydrogen at 60 p.s.i. for 1h. The solution was filtered (Celite) and concentrated to give a residue which was distilled to yield 1-methylspiro [4,4] nonane (116) (.3g, 100%) as a colourless liquid b.p. 60-65° (block)/16mm, n_D^{25} 1.4619. (Found: C, 86.8; H, 13.0. $C_{10}H_{18}$ requires C, 86.9; H, 13.1%).

Spiro [4,5] decane (117) was available from previous work in this department.

2-Methylhept-2-ene (120)

Using the procedure described for the preparation of cyclopentylcyclopentane (41), 6-methyl-6-hepten-2-one was deoxygenated to give 2-methylhept-2-ene (30%), n_D^{25} 1.4159 (lit.[95] n_D^{25} 1.4145). N.m.r.: 50 (1H, broad), 2.0-1.0 (15H, complex and overlapping). G.l.c. analysis (column G, 70°) showed the product to be pure.

Isopropylcyclopentane (121)

The potassium salt of 2-carbethoxycyclopentanone (20.8g, .107mol) was alkylated with isopropyl iodide (36.4g, .214mol) in dimethylsulphoxide (140ml), by the procedure of Pond and Cargill[103], to yield 2-isopropyl-2-carbethoxycyclopentanone (12.2g, 58%) as a yellow liquid, b.p. 70-72°/0.3mm. G.l.c. analysis (column A, 170°) showed the presence of two impurities (2 and 20% respectively), deemed to be oxygen-alkylated material.

The above impure β-~~beto~~ keto ester was decarboxylated under acidic conditions to yield 2-isopropylcyclopentanone (4.5g, 58%) as a colourless liquid b.p. 74-76°/23mm (lit.[104] 173-173.5).

Using the procedure described for the deoxygenation of 1-methyl-trans-bicyclo [4.3.0] nonan-2-one (67), 2-isopropylcyclopentanone was converted into isopropylcyclopentane (78%), which was further purified by preparative g.l.c. (column H, 90°) to yield a colourless liquid which had n_D^{20} 1.4258 (lit.[95] 1.4262). N.m.r.: 1.8-1.2 (10H complex), 0.9 (6H, doublet J 6Hz).

Pentyltriphenylphosphonium Bromide

Utilizing the procedure previously described for the preparation of pent-4-enyltriphenylphosphonium bromide, 1-bromopentane (5g) was converted into pentyltriphenylphosphonium bromide (10.6g, 84%), m.p.161-164°. (Found: C, 66.8; H, 6.3; Br, 19.2. $C_{23}H_{26}PBr$ requires C, 66.8; H, 6.3; Br, 19.3%).

Pentylidenecyclohexane (125)

Utilizing the general procedure described for the preparation of cis-deca-1,5-diene (34), the Wittig reaction between the ylid generated from pentyltriphenylphosphonium bromide (4.5g, .011mol) and cyclohexanone (1.2g, .012mol) gave pentylidenecyclohexane (125) (1g, 67%) as a colourless liquid b.p. 80° (block)/15mm, n_D^{25} 1.4621 (Found: C, 86.95; H, 13.1. $C_{11}H_{20}$ requires C, 86.8; H, 13.2%). N.m.r.:

5.0 (1H, triplet J 6Hz), 2.0 (6H, distorted broad singlet), 1.6 (10H, distorted singlet), 0.9 (3H, triplet J 5Hz). G.l.c. analysis (column G, 135°) showed the product to be homogeneous.

Cyclopentylcyclohexane (126)

A mixture of 2-cyclohexylidene-1,3-cyclopentadiene[105] (4.8g) and Adams' catalyst (.1g) in ethyl acetate (60ml) was shaken in the presence of hydrogen at 65 p.s.i. until uptake of gas ceased (1h). The solution was then filtered (Celite) and concentrated to give a residue which was distilled to yield cyclopentylcyclohexane (126) (4.1g, 82%) as a colourless liquid b.p. 87-88.5°/13mm, n_D^{20} 1.473 (lit.[106] 214°, n_D^{21} 1.473). Mass spectrum: m/e 152 (6%), 41 (100%), 39 (59%). G.l.c. analysis (column G, 135°) showed the product to be pure.

Spiro [5,5] undecane (127)

A mixture of cyclohexanone (5g, .051mol), potassium t-butoxide (11.42g, .102mol) and 1,5-dibromopentane (12.3g, .051mol) in dry benzene (100ml) was stirred and heated under reflux in an atmosphere of nitrogen for 53h. The mixture was cooled and then poured into ice-water and extracted with ether. After the ethereal extract had been washed several times with water, it was dried and concentrated to yield a yellow liquid which was distilled to give spiro [5,5] undecan-1-one (5.8g, 69%) as a colourless liquid, b.p. 53-55°/.15mm

lit.[107] 99-101/10mm). ν_{max}: 1705s. G.l.c. analysis (column A, 165°) showed the presence of an impurity (< 5%).

Using the procedure described for the preparation of cyclopentylcyclopentane (41), spiro [5,5] undecan-1-one (1g) was converted into spiro [5,5] undecane (127) (.26g, 30%), b.p. 80-85° (block)/13mm, n_D^{24} 1.475 (lit.[108] 212°, n_D^{25} 1.476). Mass spectrum: m/e 152 (15%), 41 (100%), 39 (55%). G.l.c. analysis (column G, 135°) showed the product to be > 99% pure.

10-5 WORK DESCRIBED IN CHAPTER 6

2-Methyl-3-Oxo-Methylheptanoate (129)

A mixture of 2-methylcyclohexan-1,3-dione (9.95g, .079mol), methyl iodide (12g, .084mol) and potassium methoxide (.079mol) in methanol (70ml) was heated under reflux for 6h. Methyl iodide (3g) was added and the mixture was then refluxed for a further 15h. The solution was concentrated and the residue diluted with aqueous sodium carbonate solution and then extracted with ether. The ethereal extract was washed several times with brine and then dried. Removal of the solvent left a liquid whose n.m.r. spectrum showed it to be a mixture of the required product (129) and 2,2-dimethylcyclohexan-1,3-dione (128). Accordingly, the crude product was refluxed in a solution of sodium methoxide (.002 mol) in methanol (80ml), for 1h. The mixture was then poured into water and extracted with ether. The ethereal layer was washed several times and then dried. Removal of the solvent gave a residue which was distilled to yield the keto-ester (129) (6.84g, 50%), b.p. 62^{o}/0.5mm (Found: C, 63.1; H, 9.5. $C_9H_{16}O_3$ requires C, 62.8; H,9.4%) ν_{max}: 1730s, 1705s; n.m.r.: 3.6 (3H, singlet), 2.5-1.7 (7H, complex), 1.1 (6H, doublet J 7Hz). G.l.c. analysis (column A, 150^{o}) showed the product to be homogeneous.

5-Isopropyl-Methylhex-5-enoate (130)

Using the procedure described for the preparation of the olefin (62), except the reaction mixture was stirred at room temperature for 48h, the keto-ester (129) (4g) was converted into the ester (130) (1.3g, 50% based on recovered starting material), b.p. 98-100°/18mm. (Found: C, 70.6; H, 10.5. $C_{10}H_{12}O_2$ requires C, 70.55; H, 10.7%). ν_{max} 1730s, 1640m, 900s, n.m.r.: 4.7 (2H,multiplet), 3.5 (3H, singlet), 2.3-1.5 (7H, complex), 0.9 (6H, doublet, J 7Hz).

5-Isopropyl-5-Hexen-1-ol (131)

The ester (130) (1.3g) was reduced with lithium aluminium hydride to yield 5-isopropyl-5-hexen-1-ol (131) (.66g, 66%) as a colou lessliquid b.p. 100°/18mm (Found: C, 76.3; H, 13.0. $C_9H_{18}O$ requires C, 76.0; H, 12.8%). ν_{max}: 3350s, 1640m, 900s; n.m.r.: 4.7 (2H, multiplet), 3.6 (2H, broad), 2.0 (3H, broad multiplet), 1.3 (5H, broad, one resonance disappears on addition of D_2O), 1.0 (6H, doublet J 7Hz). G.l.c. analysis(column A, 140°)showed the product to be pure

2-Isopropyl-6-Chlorohex-1-ene (132)

5-Isopropyl-5-hexen-1-ol (131) (.6g) was converted into the chloride (132) (.44g, 68%) by the usual procedure involving pyridinium chloride displacement of the p-toluenesulphonate ester. G.l.c. analysis (column G, 150°) showed the presence of a number of impurities (total 4%). The product was therefore further purified

by preparative g.l.c. (column I, 130°) to give the chloride (132) as a colourless liquid b.p. 90-95° (block)/20mm. (Found: C, 67.5; H, 10.6. $C_9H_{17}Cl$ requires C, 67.3; H, 10.7%). N.m.r.: 4.7 (2H, multiplet), 3.4 (2H, triplet J 6Hz), 2.2-1.5 (7H, complex), 1.0 (6H, doublet J 7 Hz).

5-Hexen-2-one (133)

2,4-Pentandione (27.5g) was converted into 5-hexen-2-one (13.5g, 58%) using the procedure developed by Boatman, Harris and Hauser[109]. The ketone (133) so obtained had b.p. 130-132° (lit.[110] 126-127°/745mm). ν_{max}: 1710s, 1640m, 920s; n.m.r.: 6.1-5.6(1H, complex), 5.1-4.8 (2H, complex), 2.3 (4H, v. distorted quartet), 2.1 (3H, singlet).

3-Methylhepta-2,6-diene (134) and (135)

A suspension of ethyltriphenylphosphonium iodide (25g, .06mol) and potassium t-butoxide (6.6g, .059mol) in dry ether (125ml), was stirred at room temperature for 1h. The resulting deep orange solution was then cooled to -78° and treated dropwise with a solution of 5-hexen-2-one (133) (5.8g, .059mol) in ether (50ml). The mixture was then allowed to equilibrate to room temperature over a 24h period. A working-up procedure in the usual manner (see preparation of the diene (60)) gave the diene (3.4g, 53%) as a colourless liquid b.p. 119-120°, n_D^{20} 1.4311 (Found: C, 87.0; H, 12.6.

C_8H_{14} requires C, 87.2; H, 12.8%). N.m.r.: 6.0-4.8 (4H, complex), 2.1 (4H, distorted doublet), 1.6 (6H, singlet showing fine splitting). G.l.c. analysis (column G, 70°) showed the product to be a mixture of the geometric isomers (135) and (134). (55:45 R = 1.12).

5-Methyl-5-Hepten-1-ol (136) and (137)

Using the procedure described for the preparation of the alcohol (25), the dienes (134) and (135) (2.6g) were converted into their respective alcohols (136) and (137) (1.8g, 60%), b.p. 98°/18mm. (Found: C, 75.1; H, 12.5. $C_8H_{16}O$ requires C, 74.9; H, 12.6%). ν_{max} 3300s, 1650vw, 1060s; n.m.r.: 5.3-5.0 (1H, complex), 3.5 (2H, triplet J 2Hz), 2.7 (1H, broad, removed by addition of D_2O) 2.0-1.3 (12H, complex). G.l.c. analysis (column A,140°) showed only the two isomers (136) and (137) to be present.

7-Chloro-3-Methylhept-2-ene (138) and (139)

The alcohols (136) and (137) (.65g) were converted into their respective chlorides (138) and (139) (.5g, 68%) using the general procedure described for the preparation of the chloride (30). The halides (138) and (139) had b.p. 85-90° (block)/21mm. (Found: C, 65.7; H, 10.5. $C_8H_{15}Cl$ requires C, 65.5; H, 10.3%). N.m.r.: 5.3-5.1 (1H, complex), 3.4 (2H, triplet J 7Hz), 2.2-1.4 (12H, complex). G.l.c. analysis (column G, 140°) showed only the geometric chloride isomers (138) and (139) to be present (R = 1.01).

1-Methyl-1-Isopropylcyclopentane (144)

1-Carboxy-1-methylcyclopentane[111] was esterified[112] to give a quantitative yield of the crude methyl ester, ν_{max}: 1725s. The ester was then treated with two equivalents of methyl magnesium iodide to give the tertiary alcohol (142) (90%). ν_{max}: 3400s.

The alcohol (142) (1g) was dehydrated by being heated at 180° with a trace of p-toluenesulphonic acid to give a liquid (.7g, 73%), which was further purified by preparative g.l.c. (column H, 110°) to yield 1-isopropenyl-1-methylcyclopentane (143), n_D^{20} 1.4498. (Found: C, 87.4, H, 13.3. C_9H_{16} requires C, 87.0; H, 13.0%). ν_{max}: 1640m, 900s. n.m.r.: 4.7 (2H, singlet showing very fine splitting), 1.7-1.3 (11H, complex), 1.0 (3H, singlet).

The olefin (143) was hydrogenated to yield 1-isopropyl-1-methylcyclopentane (144) in quantitative yield. The colourless liquid had n_D^{20} 1.4425 (lit.[95] n_D^{20} 1.436) and was pure by g.l.c. (column G, 90°). N.m.r.: 1.6-1.2 (9H, complex), 1.0 (3H, singlet), 0.8 (6H, doublet J 7Hz, irradiation at 96 Hz collapses doublet to singlet).

1-Ethyl-1-Methylcyclopentane (146)

To a solution of ethyl magnesium iodide (freshly prepared from magnesium (.75g, .032mol), ethyl iodide (4.5g, .032mol) and ether (15ml)) at -30° was added cuprous chloride (.1g, .001mol) followed by 3-methylcyclopent-2-enone[113] (3g, .032mol) in ether

(7ml). The temperature was allowed to equilibrate to room temperature during 1h and the reaction mixture was then worked-up in the usual manner. 3-Ethyl-3-methylcyclopentanone (145) (1.4g, 36%) was obtained as a colourless liquid b.p. 73.5-74°/21mm (lit.[114] 174°). ν_{max}: 1740s; n.m.r.: 2.3-1.3 (8H, complex), 1.0 (3H, singlet), .87 (3H, triplet J 8Hz).

The semicarbazone was obtained as a white crystalline solid m.p. 172-173° (lit.[114] 170°).

The ketone (145) was deoxygenated, using the conditions described for the preparation of the hydrocarbon (56), to give 1-ethyl-1-methylcyclopentane (146) (60%) as a colourless liquid n_D^{20} 1.4261 (lit.[95] n_D^{20} 1.4272). G.l.c. analysis (column G,70°) showed the product to be homogeneous.

2-Methyl-3-Methyleneheptane (150)

Using the general procedure described for the preparation of the alcohol (96), the reduction of isobutyraldehyde (5g) with n-butylmagnesium bromide gave a crude product which was oxidized by the procedure of Brown[93] to yield 2-methylheptan-3-one (5.6g, 64%) as a slightly yellow liquid b.p. 58-60°/20mm (lit.[115] 159-160°). ν_{max}: 1705s; G.l.c. analysis (column G, 90°) showed the product to be > 98% pure.

Using the procedure described for the preparation of the olefin (62), 2-methylheptan-3-one (1g) was converted into 2-methyl-3-methyleneheptane (150) (.8g, 80%). A sample isolated by preparative g.l.c. (column H, 105°) had n_D^{20} 1.4198 (Found: C, 85.5; H, 14.1. C_9H_{18} requires C, 85.6; H, 14.4%). N.m.r.: 4.83 (2H, multiplet), 2.0 (3H, broad multiplet), 1.3 (4H, broad multiplet), 1.1-0.9 (9H, complex).

Isopropylcyclohexane (151)

4-Isopropyl-2-cyclohexen-1-ol (2g) was hydrogenated to give a quantitative yield of 4-isopropylcyclohexanol. The crude alcohol was then oxidized[93] to give 4-isopropylcyclohexanone (1.38g, 68%) as a slightly yellow liquid b.p. 96-100°/18mm (lit.[116] 139-140°/100mm). ν_{max} 1710s. G.l.c. analysis (column A, 140°) showed an impurity (5%).

Following the procedure for the preparation of the hydrocarbon (56), 4-isopropylcyclohexanone (.92g) was converted into isopropyl cyclohexane (151) (.8g, 88%), b.p. 50-55° (block)/20mm (lit.[95] 154.763 G.l.c. analysis (column G, 90°) showed an impurity (5%) to be present. Preparative g.l.c. (column H, 105°) gave a pure sample which had n_D^{20} 1.4412 (lit.[95] n_D^{20} 1.4409).

3-Methylhept-2-ene (140) and (141)

Using the procedure described for the preparation of the dienes (134) and (135), 2-hexanone (1g) was converted into 3-methylhept-2-ene (140) and (141) (.95g, 95%). A sample isolated by preparative g.l.c. (column H, 90°) had n_D^{20} 1.4189 (lit.[95] n_D^{20} 1.419). N.m.r.: 5.3-5.0 (1H, complex), 2.0 (2H, broad), 1.7-1.3 (10H, complex), 0.9 (3H, triplet J 4Hz). G.l.c. analysis (column G, 70°) showed the sample to be a mixture of geometric isomers (1:1, R = 1.12).

trans-1,2-Dimethylcyclohexane (156) and cis-1,2-Dimethylcyclohexane (157)

2-Methylcyclohexanone (2g) was converted into 1-methylene-2-methylcyclohexane, which was hydrogenated to yield a 3:2 mixture of the cis and trans isomers (157) and (156). The isomers were separated by preparative g.l.c. (column H, 90°) and had the following constants.

trans-1,2-dimethylcyclohexane (156) n_D^{20} 1.4269 (lit.[75] 1.42695)

cis-1,2-dimethylcyclohexane (157) n_D^{20} 1.4349 (lit.[95] 1.4345

10-6 WORK DESCRIBED IN CHAPTER 7

1-(4'-Chlorobut-1'-yl)cyclopentene (160) and 2-(3'-Bromopropyl) methylenecyclohexane (161) were kindly donated by Dr. G.E. Gream.

2-(3'-Bromopropyl)methylenecyclopentane (162)

3-(2'-Methylenecyclopentyl)propyl p-nitrobenzene sulphonate, m.p. 56-57.5° (lit.[117] 59°) was converted into the bromide (162) (76%), using the procedure described for the preparation of the bromide (28). The required bromide (162) was obtained as a colourless liquid b.p. 65-70° (block)/1.0mm. (Found: C, 53.2; H, 7.3. $C_9H_{15}Br$ requires C, 53.2; H, 7.4%). N.m.r.: 4.7 (2H, distorted quartet J ≃ 2Hz), 3.3 (2H, triplet J 7Hz), 2.5-1.2 (11H, complex). G.l.c. analysis (column A, 135°) showed the product to be pure.

1-Butylcyclopentene (166)

1-Butylcyclopentanol, prepared from the treatment of cyclopentanone (5g) with butyl magnesium bromide, was heated with oxalic acid dihydrate (7g) in dimethyl sulphoxide (20ml) and water (1.5ml) at 110° under nitrogen for 40h. The cooled solution was diluted with light petroleum and poured into ice-water. The light petroleum extract was washed with aqueous sodium carbonate, water and then dried. The solution was concentrated to give a black residue which was chromatographed on Sorbsil. Elution with light

petroleum gave 1-butylcyclopentene (166) (3.5g, 42%) as a colourless liquid. G.l.c. analysis (column D, 140°) showed an impurity (8%) assumed to be butylidenecyclopentane. A pure sample of the olefin (166) obtained by preparative g.l.c. (column E, 90°) had n_D^{25} 1.4456 (lit.[95] 1.4463). N.m.r: 5.3 (1H, distorted triplet J 1Hz), 2.5-1.0 (15H, complex).

Spiro [4,4] nonane (167)

Using the procedure described for the preparation of cyclopentylcyclopentane (41), spiro [4,4] nonan-1-one (4.5g) was converted into spiro [4,4] nonane (167) (2.4g, 60%), b.p. 55-60° (block)/14mm, n_D^{25} 1.4588 (lit.[118] 156.2-157.7/748mm, n_D^{20} 1.4618). Mass spectrum: m/e 124 (16%), 82 (95%), 67 (100%). G.l.c. analysis (column D, 140°) showed the product to be pure.

trans-Bicyclo [4.3.0] nonane (168)

Using the previous procedure trans-bicyclo [4.3.0] nonan-2-one (64) (1g) was deoxygenated to yield trans-bicyclo [4.3.0] nonane (168) (.5g, 56%), n_D^{25} 1.4616 (lit.[119] n_D^{25} 1.4616).

cis-Bicyclo [4.3.0] nonane (169)

The high pressure hydrogenation of indane with Raney nickel catalyst, gave a crude product which was purified by preparative g.l.c (column E, 110°) to yield pure cis-bicyclo [4.3.0] nonane (169),

n_D^{25} 1.4697 (lit.[119] n_D^{25} 1.4700).

1-Methylene-2-Propylcyclohexane (174)

Using the procedure described for the preparation of the olefin (62), 2-propylcyclohexanone (1.9g) was converted into 1-methylene-2-propylcyclohexane (174) (1.5g, 79%) b.p. 85° (block)/24mm, n_D^{25} 1.4558. (Found: C, 86.8; H, 12.9. $C_{10}H_{18}$ requires C, 86.9; H, 13.1%). ν_{max}: 1645m, 900s; n.m.r.: 4.5 (2H, singlet), 2.2-0.9 (16H, complex); mass spectrum: m/e 138 (5%), 96 (100%). G.l.c. analysis (column D, 140°) showed the product to be pure.

3a-Methyl-cis-Bicyclo [4.3.0] nonane (176)

An authentic sample was kindly donated by Dr. I. Buczysnki.

1-Methylene-2-Propylcyclopentane (179)

The potassium salt of 2-carbethoxycyclopentanone was alkylated with n-propyl iodide in the usual manner[103] and the resultan β-keto ester decarboxylated under acidic conditions to yield 2-propylcyclopentanone (68%) as a colourless liquid, b.p. 78-79°/22mm. (lit.[12] 70°/15mm).

Utilizing the Wittig reaction developed for the preparation of the olefin (62), 2-propylcyclopentanone (1.5g) was converted into 1-methylene-2-propylcyclopentane (179) (1.2g, 80%), b.p. 45-50° (block 20mm. (Found: C, 87.2; H, 12.6; C_9H_{16} requires C, 87.0; H, 13.0%).

ν_{max}: 1640m, 880s; n.m.r.: 4.7 (2H, distorted quartet J ≃ 2Hz), 2.4-0.8 (14H, complex); mass spectrum: m/e 124 (5%), 82 (100%), 81 (93%). G.l.c. analysis (column D, 140°) showed the presence of an impurity (8%) assumed to be 1-methyl-2-propylcyclopentene.

CHAPTER 11

GAS LIQUID CHROMATOGRAPHY

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GAS LIQUID CHROMATOGRAPHY

11-1 QUALITATIVE G.L.C.

Chromatographic methods of qualitative analysis have considerable advantages over other methods, in that it is possible to investigate rapidly and simply the composition of a mixture without resort to other physical or chemical methods.

Conventional qualitative g.l.c. analysis is based on the comparison of the retention time or volume of an unknown compound, with respective data obtained under identical conditions for a known compound. This type of comparison with one column, however, cannot be considered as a method of identification, since it allows the "identification" of already known substances, but it definitely indicates the absence of particular substances in the case of non-agreement of the compared values.

This method can be authenticated if the specific retention volumes deduced from the retention times and all the experimental parameters are used. The calculation of specific retention volumes however is difficult to achieve and usually relative values of time and volume are used.

The reliability of such identifications is directly dependent on the efficiency of the column used, since as the number

of theoretical plates of a column increase, the probability of superimposition of peaks correspondingly decreases.

It has been stated[121] that such identifications on one column are only valid when the number of theoretical plates (n) exceeds 10^5.

Even if the substances are chromatographed on two columns the same principles apply, and it must be noted that for certain isomers which are chemically very similar, the usual practice of changing the stationary phase does not give the desired effect.

Characterization of a Peak

The chromatographic peak is characterized by its retention time (t_r), the time (or distance on the recorder chart) between the point of injection and the peak maximum.

The retention of an inert component (i.e. the air-peak or the gas-holdup of the column) is denoted by t_m. The time spent by the substance in the liquid phase alone is then called the adjusted retention time (t_R).

$$t_R = t_r - t_m$$

The Partition Process

The partition (capacity) ratio (k) expresses the equilibriu ratio of the amounts of sample component in the stationary and gas phases of the column.

$$k = \frac{t_r - t_m}{t_m} = \frac{t_R}{t_m}$$

$$\therefore \quad t_r = t_m(1 + k)$$

Peak Separation

In any chromatogram the relative position of two consecutive peaks is expressed by the relative volatility or relative retention (α).

$$\alpha = \frac{t_{R_2}}{t_{R_1}} = \frac{k_2}{k_1}$$

where $t_{R_2} > t_{R_1}$

This value however does not express the true separation of the two peaks because the characteristics of the peaks are not taken into account. The true separation of two consecutive peaks is expressed by the peak resolution (R).

$$R = \frac{t_{R_2} - t_{R_1}}{\frac{1}{2}(W_{b_1} + W_{b_2})} = \frac{2\Delta t}{W_{b_1} + W_{b_2}}$$

W_b = base width or intercept (the distance along the baseline between the intercepts of the tangents drawn through the inflection points of the Gaussian peak).

If the two peaks are poorly resolved then $W_{b_1} \simeq W_{b_2}$ and

$$R \simeq \frac{\Delta t}{W_{b_2}}$$

If R = 1, the resolution of two equal area peaks is about 98%, while R = 1.5 represents 99.7% resolution or complete base-line separation.

Column Efficiency

The number of theoretical plates (n) expresses the efficiency of any column

$$n = 16\left(\frac{t_r}{W_b}\right)^2 = 5.54\left(\frac{t_r}{W_h}\right)^2$$

Wh = half-width (measured at half the height of the Gaussian peak).

The theoretical plate is a hypothetical part of the column in which equilibrium is established during the partition process.

The height equivalent to a theoretical plate (HETP) is then defined as the length of a column, in which theoretically, a single equilibrium between gas and liquid phases is established.

$$HEPT = \frac{L}{n}$$

The preceding terms may be related, to calculate the number of theoretical plates required, ($n_r eq$) in order to achieve a desired resolution (R*), for a given component pair defined by α

k (refer to second peak).

$$n_{req} = 16R^{*2}\left(\frac{\alpha}{\alpha - 1}\right)^2 \left(\frac{k + 1}{k}\right)^2$$

Flow Rate and Gas Velocity

The carrier gas velocity at the column outlet (U_o) corrected to column temperature, is derived from the flow rate (F_c).

For packed columns $U_o = \frac{F_c}{\varepsilon r^2 \pi}$

r = column radius

ε = interparticle porosity or the fraction of the column cross-section available for moving carrier gas

For open tubular columns $U_o = \frac{F_c}{r^2 \pi}$

The average linear gas velocity ($\bar{U}$) may be calculated from the column length (L) and the air-peak (t_m), provided the volume of "dead space" in the instrument is negligible.

$$\bar{U} = \frac{L}{t_m}$$

The Basic Golay Equation

Golay[122,123] developed the following equation for HETP in terms of the average linear gas velocity ($\bar{U}$) to explain the theory of open tubular columns.

$$HETP = \frac{B}{\bar{U}} + C_G \bar{U} + C_L \bar{U}$$

which has a HETP minimum at an optimum average linear gas velocity ($\bar{U}_{opt}$)

$$HETP_{min} = 2\sqrt{B(C_L + C_G)}$$

this expression may be simplified to

$$HETP_{min} = \sqrt{\frac{1+ 6k + 11k^2}{3(1 + k)^2}} \times r$$

Therefore the best capillary column performance is directly determined by its diameter.

$$HETP_{min} = 1.91r \simeq 1.d \quad \text{(where } k \geqslant 1000\text{)}$$

An expression for the OPGV may also be derived.

$$\bar{U}_{opt} = \sqrt{\frac{B}{C_G + C_L}}$$

which simplifies to

$$\bar{U}_{opt} = \frac{4D_G}{r} \sqrt{\frac{3(1 + k)^2}{1 + 6k + 11k^2}}$$

typical values of D_G are

in H_2 $\sim$ .1 $cm^2\ sec^{-1}$

other gases $\sim$ .04 $cm^2\ sec^{-1}$

therefore the OPGV for which a maximum column efficiency is obtainable

is

$$\bar{U}_{opt} \sim \frac{4}{d} \text{ cm sec}^{-1} \quad (H_2)$$

$$\sim \frac{.2}{d} \text{ cm sec}^{-1} \quad \text{(other gases)}$$

Modified Expressions related to the Plate Number Concept

It is evident that for open tubular columns the long gas-hold up time (t_m) will falsely increase the number of theoretical plates (n), although not contributing to its efficiency.

To avoid this difficulty the number of effective plates (N) has been related to the basic term (n)[124].

$$N = n\left(\frac{k}{k+1}\right)^2$$

For packed columns, k is fairly large and therefore $N \rightarrow n$, with open tubular columns, if k is small, N will only be a fraction of n.

Desty and his co-workers[124] have also defined an expression of the height equivalent to one effective plate (HEETP).

$$\text{HEETP} = \frac{L}{N} = \text{HETP}\left(\frac{1+k}{k}\right)^2$$

HEETP vs $\bar{U}$ curves may be drawn, and they look very similar to the HETP vs $\bar{U}$ plots. From these curves the optimum practical gas velocity (OPGV) can be obtained as the point on the curve at which the line drawn to the origin has a minimum slope.

Publication of Retention Data

The Discussion Group of the Institute of Petroleum[125] has made the following recommendations for the standardization of retention data.

(1) only adjusted retention times (t_R) should be used.

(2) the retention data should be published in the form of the retention index (I).

(3) the slope (b) of the log (retention volume) against carbon number for a minimum of these n-alkanes should be quoted with all data.

In the"retention index" system of Kovats[126], the logarithmic retention of a substance is interpolated between those of two standard compounds. The retention index (I) is defined by the equation

$$I = 100.\ \frac{\log\ (r_x/r_n)}{\log\ (r_{n+1}/r_n)} + 100n$$

where r_x, r_n, r_{n+1} are the adjusted retention times of the unknown compound and the n-alkanes of carbon number n and n+1.

$$b = \frac{\log\ r_{n+1} - \log\ r_n}{n}$$

Experimental

The hydrocarbons were prepared by synthetic methods or obtained commercially.

The gas chromatogram used was a Perkin-Elmer, Model 881, equipped with a flame ionization detector. The determinations were performed in a stainless steel open tubular column of .508mm id x 100m, coated with Apiezon L. Nitrogen was used as the carrier gas.

The OPGV for this column was determined by a plot of HEETP vs $\bar{U}$, for the n-heptane and n-octane peaks at a column oven temperature of 75^{o}.

An OPGV value of $\simeq$ 7.5cm sec^{-1} was obtained (Fig. 10). This value was not practical however for the higher carbon number hydrocarbons.

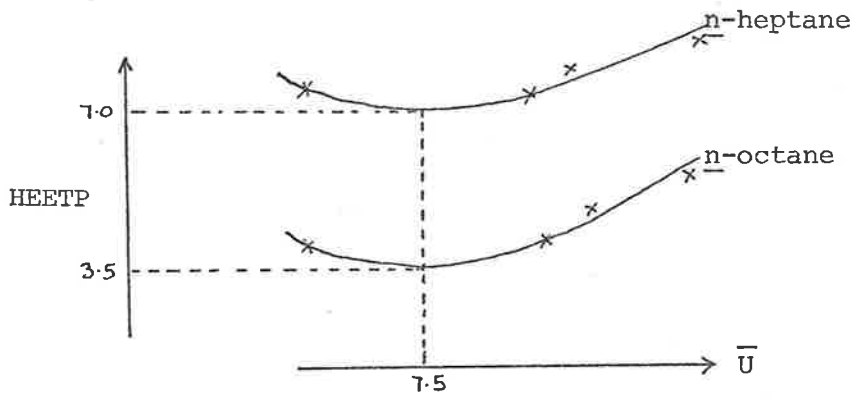

Fig. 10

The retention of the gas-hold up peak (t_m) was determined by the method of Peterson and Hirsch[127].

Retention Indices

Table 24

Retention Indices of C_7-C_8 Hydrocarbons[a,b,c]

Hydrocarbon	I
(80)	683
(81)	703
(82)	741
(83)	747
(111)	749
(107)	780
(135)	781
(141)	793
(134)	794
(120)	795
(140)	802
(112)	808
(146)	810
(156)	822
cycloheptane	822
(121)	833
(157)	851

(cont. page 158).

a.

	n	k	N
n-heptane	196,000	.3912	15,500
n-octane	150,000	.6679	32,700

b. Temp = 75^{o}, $\overline{U}$ = 7.1 cm sec^{-1}

c. b = .3533.

Table 25

Retention Indices of C_9 Hydrocarbons[a,b,c]

Hydrocarbon	I
(150)	845
(88)	887
(89)	902
(143)	917
(144)	921
(180)	924[d]
(179)	931
(90)	936
cis-2-methyl-cis-bicyclo [3.3.0]octane	948[d]
(151)	950
trans-1-methyl-cis-bicyclo[3.3.0]octane	951[d]
(91)	956
(166)	959
(167)	975
cis-1-methyl-cis-bicyclo[3.3.0]octane	981[d]
(168)	996
(169)	1030

(cont. page 160).

a.

	n	k	N
n-nonane	148,000	.6764	39,400
n-decane	120,000	.8418	57,200

b. Temp = 92^{o}; $\overline{U}$ = 11.9 cm sec^{-1}

c. b = .3180

d. the calculated I value of (180), based on the three methyl bicyclo[3.3.0]octanes was the same as the actual value determined from the reaction mixtures.

Table 26

Retention Indices of C_{10}-C_{11} Hydrocarbons[a,b,c]

Hydrocarbon	I
(33)	974
(34)	974
(174)	1035
(38)	1045
(37)	1051[d]
(56)	1055[d]
1-methylene spiro[4.4]nonane	1064
(175)	1066 ± 3[e]
(116)	1074
(176)	1084
(58)	1090
(57)	1096
trans (62)	1103
(117)	1112
cis (62)	1116
(74)	1119[f]
(59)	1123[f]
(41)	1129
(125)	1159
(75)	1163

(cont. page 162).

Hydrocarbon	I
(127)	1235
(126)	1240

a.

	n	k	N
n-decane	190,000	.9886	46,500
n-undecane	149,000	1,902	64,000
n-dodecane	145,000	3,630	89,200

b. Temp = 115°; $\bar{U}$ = 11.1 cm sec^{-1}

c. b = .2814

d. R = 1.36

e. calculated from available data; see ref 62

f. R = 1.23

11-2 QUANTITATIVE G.L.C.

Accurate peak area measurements are dependent on the quality of the g.l.c. data available. The g.l.c. apparatus and analytical conditions must accordingly satisfy certain requirements.

The flow rate must be constant, so that the desired retention parameters may be accurately calculated.

The detector response must be linear over the range of sample concentration studied.

Detector response may vary for different substances, but the response (or calibration) factors necessary to correct for this have to be known.

Only the measurement of peak area may be considered adequate for quantitative curve interpretation and each consecutive peak must be separated by a substantial section of the base line.

The peak areas, in this study, were determined with a Perkin-Elmer 194B printing integrator connected to a Honeywell recorder. The accuracy using this type of integrator, however, is affected by peak attenuation and the interpretative skill of the operator,. Added to these difficulties is the fact that a ball and disc integrator can never be more accurate than the recorder from which it receives its signal.

In an attempt to minimize such errors, the determinations for any one run were repeated until the values between successive determinations were in close agreement.

The detector response was calculated for several of the hydrocarbons relative to the internal standard which was always of the same carbon number and non-aromatic. These values were found to be close to unity. This is in agreement with previous work[128] which indicates that isomeric hydrocarbons (excluding aromatics) have very similar detector responses.

REFERENCES

REFERENCES

1. S. Arai, S. Sato and S. Shida, J. Chem. Phys., 33, 1277 (1960).
2. A.S. Gordon and S.R. Smith, J. Phys. Chem., 66, 521 (1962).
3. R.C. Lamb, P.W. Ayers and M.K. Toney, J. Amer. Chem. Soc., 85, 3483 (1963).
4. C. Walling and M.S. Pearson, J. Amer. Chem. Soc., 86, 2262 (1964).
5. R.G. Garwood, C.J. Scott and B.C.L. Weedon, Chem. Commun., 14 (1965).
6. (a) J.F. Garst, P.W. Ayers and R.C. Lamb, J. Amer. Chem. Soc., 88, 4260 (1966).
   (b) J.F. Garst and F.E. Barton, II, Tetrahedron Lett., 587 (1969).
7. (a) R.C. Lamb, P.W. Ayers, M.K. Toney and J.F. Garst, J. Amer. Chem. Soc., 88, 4261 (1966).
   (b) C. Walling and A. Cioffari, ibid., 92, 6602 (1970).
8. C. Walling, J.H. Cooley, A.H. Ponaras and E.J. Racah, J. Amer. Chem. Soc., 88, 5361 (1966).
9. J.K. Kochi and J.W. Powers, J. Amer. Chem. Soc., 92, 137 (1970).
10. H. Hart and D. Wyman, J. Amer. Chem. Soc., 81, 4891 (1959).
11. (a) J.K. Kochi and P.J. Krusic, J. Amer. Chem. Soc., 91, 3940 (1969).
   (b) R.A. Sheldon and J.K. Kochi, ibid., 92, 4395 (1970).
12. D.J. Edge and J.K. Kochi, J. Amer. Chem. Soc., 94, 7695 (1972).

13. L.K. Montgomery and J.W. Matt, J. Amer. Chem. Soc., 89, 3050, 6556 (1967).

14. (a) G. Butler and R.J. Angelo, J. Amer. Chem. Soc., 79, 3128 (1957).

(b) G. Butler, A. Crawshaw and W.L. Miller, ibid., 80, 3615 (1958).

15. (a) C.S. Marvel and R.D. Vest, J. Amer. Chem. Soc., 79, 5771 (1957).

(b) C.S. Marvel and J.K. Stille, ibid., 80, 1740 (1958).

(c) C.S. Marvel and E.J. Gall, J. Org. Chem., 25, 1784 (1960).

16. W.S. Friedlander and G. van D. Tiers, Ger. Pat. 1098942 (Chem. Abstr., 56, 5810 (1962)).

17. (a) N.O. Brace, J. Amer. Chem. Soc., 86, 523 (1964).

(b) N.O. Brace, J. Org. Chem., 31, 2879 (1966).

(c) N.O. Brace, ibid., 34, 2441 (1969).

(d) N.O. Brace, ibid., 36, 3187 (1971).

18. J.I.G. Cadogan, M. Grumbaum, D.H. Hey, A.S.H. Ong and J.T. Sharp, Chem. Ind., (London), 422 (1968).

19. N.O. Brace, J. Org. Chem., 38, 3167 (1973).

20. N.O. Brace, J. Polym. Sci., Part A-1, 8, 2091 (1970).

21. M. Julia and M. Maumy, Bull. Soc. Chim. Fr., 2415 (1969).

22. R. Dulov, Y. Chretien-Bessiere and H. Desalbres, C.R. Acad. Sci., 258, 603 (1964).

23. J.P. Montheard, ibid., 260, 577 (1965).

24. Z. Cekovic, Tetrahedron Lett., 749 (1972).

25. H.G. Kuivila and E.J. Walsh, Jr., J. Amer. Chem. Soc., 88, 571, 576 (1966).

26. M. Julia and M. Maumy, Bull. Soc. Chim. Fr., 2427 (1969).

27. S. Winstein, R. Heck, S. Lapporte and R. Baird, Experientia, 12, 138 (1956).

28. D.F. deTar and C. Weiss, J. Amer. Chem. Soc., 78, 4296 (1956).

29. P.J. Bunyan and D.H. Hey, J. Chem. Soc., 1360 (1962).

30. M. Julia and D. Mansuy, C.R. Acad. Sci., Ser. C., 269, 1568 (1969

31. (a) R. Breslow, J.T. Groves and S.S. Olin, Tetrahedron Lett., 4717 (1966).

(b) Idem, ibid., 1837 (1968).

32. D.L. Struble, A.L.J. Beckwith and G.E. Gream, Tetrahedron Lett., 4795 (1970).

33. M. Julia, Accounts Chem. Res., 4, 386 (1971).

34. M. Julia, F. Le Goffic and Katz, Bull. Soc. Chim. Fr., 1122 (1964).

35. M. Julia, J-C. Chottarel and J.S. Basselier, Bull. Soc. Chim. Fr., 3037 (1966).

36. T.W. Sam and J.K. Sutherland, Chem. Commun., 970 (1971).

37. For reviews of this work see ref. 33 and also:

(a) M. Julia, Rec. Chem. Progr., 25, 1 (1964).

(b) M. Julia, Pure Appl. Chem., 15, 167 (1967).

38. M. Julia, J-M. Surzur and L. Katz, Bull. Soc. Chim. Fr.,

1109 (1964).

39. (a) H.G. Kuivila, L.W. Menapace and C.R. Warner, J. Amer. Chem. Soc., 84, 3584 (1962).

(b) H.G. Kuivila and L.W. Menapace, ibid., 86, 3047 (1964).

40. (a) A.L.J. Beckwith and W.B. Gara, J. Amer. Chem. Soc., 91, 5689, 5691 (1969).

(b) W.B. Gara, Ph.D. Thesis (1970), University of Adelaide.

41. D.L. Struble, A.L.J. Beckwith and G.E. Gream, Tetrahedron Lett., 3701 (1968).

42. A.L.J. Beckwith, Spec. Publs. Chem. Soc., No. 24, 239 (1970).

43. J.W. Wilt, S.N. Massie and R.B. Dabek, J. Org. Chem., 35, 2803 (1970).

44. K.W. Watkins and D.K. Olsen, J. Phys. Chem., 76, 1089 (1972).

45. H.G. Kuivila, Accounts Chem. Res., 1, 299 (1968).

46. D.J. Carlsson and K.U. Ingold, J. Amer. Chem. Soc., 90, 7047 (1968).

47. For leading references see ref. 45.

48. R.B. Holloway, B.Sc.(Hons), Thesis (1971) University of Adelaide.

49. G. Moad, B.Sc.(Hons) Thesis (1973) University of Adelaide.

50. C. Walling and A. Cioffari, J. Amer. Chem. Soc., 94, 6059 (1972).

51. M. Schlosser in "Topics in Stereochemistry", eds. N. Allinger and E.L. Eliel, Interscience, New York, Vol. 5, p. 1 (1970).

52. R.T. Blickenstaff and F.C. Chang, J. Amer. Chem. Soc., 80, 2726 (1958).

53. M. Tamura and J. Kochi, Synthesis, 6, 303 (1971).

54. W.S. Johnson, et al, J. Amer. Chem. Soc., 86, 1959 (1964).

55. W.S. Johnson and J.K. Crandall, J. Org. Chem., 30, 1785 (1965).

56. G.A. Wiley, R.L. Hershkowitz, B.M. Rein and B.C. Chung, J. Amer. Chem. Soc., 86, 964 (1964).

57. L.I. Smith and J.S. Swenson, J. Amer. Chem. Soc., 79, 2962 (1957).

58. I.M. Downie, J.B. Holmes and J.B. Lee, Chem. Ind. (London), 900 (1966).

59. E.S. Kosower and S. Winstein, J. Amer. Chem. Soc., 78, 4354 (1956).

60. Comment by Dr. R.H. Prager, at a seminar given on this topic.

61. V.N. Drozd, Y.A. Ustynyuk, M.A. Tseleva and L.B. Dimitriev, J. Gen. Chem. USSR, 39, 1951 (1969).

62. I.M. Makarova, V.A. Zaklarenko and A.A. Petrov, Neftekhimiya, 7, 491 (1967).

63. R. Schimpt and P. Heimbach, Chem. Ber., 103, 2122 (1970).

64. N.O. Brace, J. Org. Chem., 32, 2711 (1967).

65. Dr. I.A. Blair, Postdoctoral Fellow 1973-1974.

66. R.B. Woodward and R. Hoffmann, Angew. Chem., 81,797 (1969).

67. A.L.J. Beckwith, G.E. Gream and D.S. Struble, Austral. J. Chem.,

25, 1081 (1972).

68. R. Hoffmann, Accounts Chem. Res., 4, 1 (1971).

69. R. Hoffmann, C.C. Levin and R.H. Moss, J. Amer. Chem. Soc., 95, 629 (1973).

70. W.S. Johnson and R. Owyang, J. Amer. Chem. Soc., 86, 5593 (1964).

71. G. Schomburg and G. Dielmann, J. Chromatog. Sci., 11, 151 (1973).

72. E. Bendel, H. Huber, W. Meltzuwand and A. Lorenz, J. Chromatog., 38, 388 (1968).

73. C.F. Pincombe, Ph.D. Thesis (1973), University of Adelaide.

74. J. Knotnerus and H. Schilling. Rec. Trav. Chim., 83, 414 (1964).

75. P.D. Bartlett, R.E. Pincock, J.H. Rolston, J.H. Schindel and L.H. Singer, J. Amer. Chem. Soc., 87, 2590 (1965).

76. F.D. Greene and N.N. Lowry, J. Org. Chem., 32, 882, 875 (1967).

77. K.U. Ingold in "Free Radicals", ed. J.K. Kochi, Wiley Interscience, New York, Vol. I, p. 37 (1973).

78. R.D. Rieke and N.H. Moore, Tetrahedron Lett., 2035 (1969).

79. H. Fujimoto, S. Tamabe, T. Minato and K. Fukui, J. Amer. Chem. Soc 94, 9205 (1972).

80. A.L.J. Beckwith and G. Phillipou, Chem. Comm., 658 (1971).

81. H.C. Brown and G.J. Zweifel, J. Amer. Chem. Soc., 83, 1241 (1961)

82. F. Sondheimer and Y. Gaoni, J. Amer. Chem. Soc., 84, 3520 (1962).

83. L.F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Interscience, New York, Vol. I, p. 1180 (1967).

84. J.G. Traynham and O.S. Pascval, J. Org. Chem., 21, 1362 (1956).

85. Chem. Abstr., 69, 10788b (1968).

86. R.G. Lawton, J. Amer. Chem. Soc., 83, 2399 (1961).

87. E.R. Shepard and J.F. Noth, J. Org. Chem., 19, 415 (1954).

88. G.E. Coheen, J. Amer. Chem. Soc., 63, 744 (1941).

89. I.J. Borowitz et al, J. Org. Chem., 37, 581 (1972).

90. D.W. Mathieson, J. Chem. Soc., 3248 (1953).

91. C. Ainsworth, Org. Syn., Col. Vol. 4, 536 (1963).

92. W. Huckell, W. Egerer and F. Mossner, Justus Leibigs Ann. Chem., 645, 162 (1961).

93. H.C. Brown and C.P. Garg, J. Amer. Chem. Soc., 83, 2952 (1961).

94. G. Stork and S.R. Dowel, J. Amer. Chem. Soc., 85, 2178 (1963).

95. Selected values of Physical and Thermodynamic Properties of Hydrocarbons and Related Compounds, American Petroleum Institute Research Project 44.

96. J. Colonge and P. Lasfargues, Bull. Soc. Chim. Fr., 177 (1962).

97. G. Wittig and D. Wittenberg, Justus Leibigs Ann. Chem., 606, 1 (1957).

98. G.F. Woods, Jr., Org. Syn., 27, 43 (1947).

99. R. Ganger, H. Techner and M. Delepine, C.R. Acad. Sci., 250, 1282 (1960).

100. V.M. Micovic and M.L. Mihailovic, J. Org. Chem., 18, 1190 (1953).

101. J.H. Mathews and P.R. Fehlandt, J. Amer. Chem. Soc., 53, 3212 (1931).

102. W.E. Doering and F.M. Beringer, J. Amer. Chem. Soc., 71, 2221 (1949).

103. D.M. Pond and R.L. Cargill, J. Org. Chem., 32, 4064 (1967).

104. F.C. Kornfeld, R.G. Jones and T.V. Parke, J. Amer. Chem. Soc., 71, 150 (1949).

105. E.P. Kohler and J. Kable, J. Amer. Chem. Soc., 57, 917 (1935).

106. N.D. Zelinsky and I.N. Titz, Ber. dtsch. chem. Ges., 64, 183 (1931).

107. H.A.P. DeJongh and H. Wynberg, Tetrahedron, 20, 2553 (1964).

108. A. Dixon and P.A. Naro, J. Org. Chem., 25, 2094 (1960).

109. S. Boatman, T.M. Harris and C.R. Hauser, J. Org. Chem., 30, 3321 (1965).

110. M.S. Schechter, N. Green and F.B. LaForge, J. Amer. Chem. Soc., 71, 3168 (1949).

111. H. Koch and W. Haaf, Justus Leibigs Ann. Chem., 618, 251 (1958).

112. J.L. Marshall, K.C. Erickson and T.K. Folsom, Tetrahedron Lett., 4011 (1970).

113. R.H. Acheson and R. Robinson, J. Chem. Soc., 1127 (1952).

114. J.V. Braun, W. Keller and K. Weissbach, Justus Leibigs Ann. Chem.

490, 179 (1931).

115. R.H. Prickard and J. Kenyon, J. Chem. Soc., 101, 620 (1912).

116. R.S. Cohn, H.R. Penfold and J.L. Simonsen, J. Chem. Soc., 1366 (1931).

117. A.K. Serelis, B.Sc.(Hons) Thesis (1970), University of Adelaide.

118. Chem. Abstr., 41, 3769b (1947).

119. N.L. Allinger and J.L. Coke, J. Amer. Chem. Soc., 82, 2553 (1960)

120. J.G. Hilderbrand and M.T. Bogert, J. Amer. Chem. Soc., 58, 650 (1936).

121. V.G. Arakelyan and K.I. Sakodynskii, Chromatogr. Rev., 15, 93 (1971).

122. M.J.E. Golay in "Gas Chromatography", eds. V.J. Coates, H.J. Nobe and I.S. Fagerson, Academic Press, New York, p. 1 (1958).

123. M.J.E. Golay in "Gas Chromatography 1958", ed. D.H. Desty, Butterworths, London, p. 36 (1958).

124. D.H. Desty, A. Goldup and W.T. Swanton in "Gas Chromatography", eds. N. Brenner, J.E. Callen and M.D. Weiss, Academic Press, New York, p. 105 (1962).

125. "Gas Chromatography", ed. A. Goldup, Butterworths, London, p. 348 (1965).

126. E. Sz. Kovats, in "Advances in Chromatography", eds. J.C. Gidding and R.A. Keller, Dekker, New York, Vol. I, p. 229 (1965), and references cited therein.

127. M.L. Peterson and J. Hirsch, J. Lipid. Res., 1, 132 (1959).

128. J.W. Carson, G. Lege and J.D. Young, J. Chromatog. Sci., 11, 503 (1973).

129. H.O. House and G.H. Rasmusson, J. Org. Chem., 28, 31 (1963)

130. B. Capon, Quart. Review, (London) 18, 45 (1964)